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Edited by Frank E. Hytten

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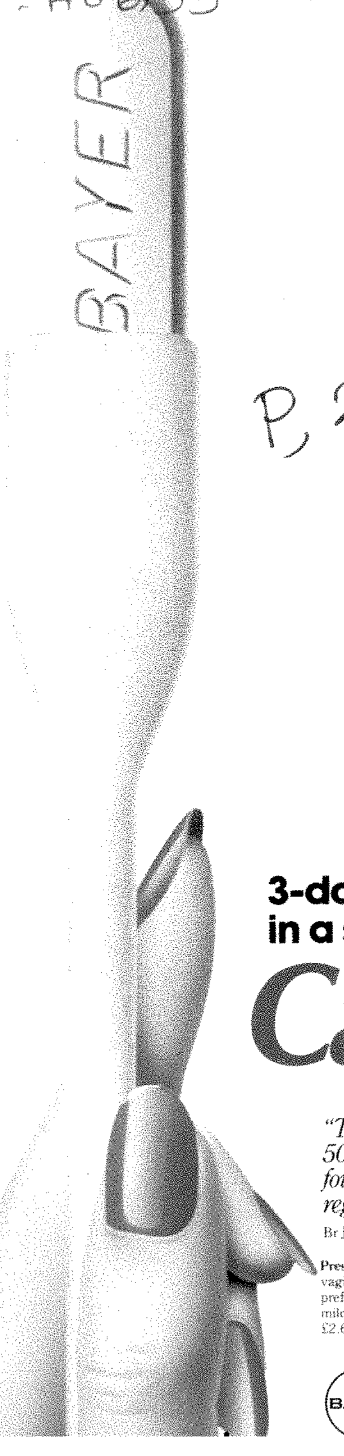

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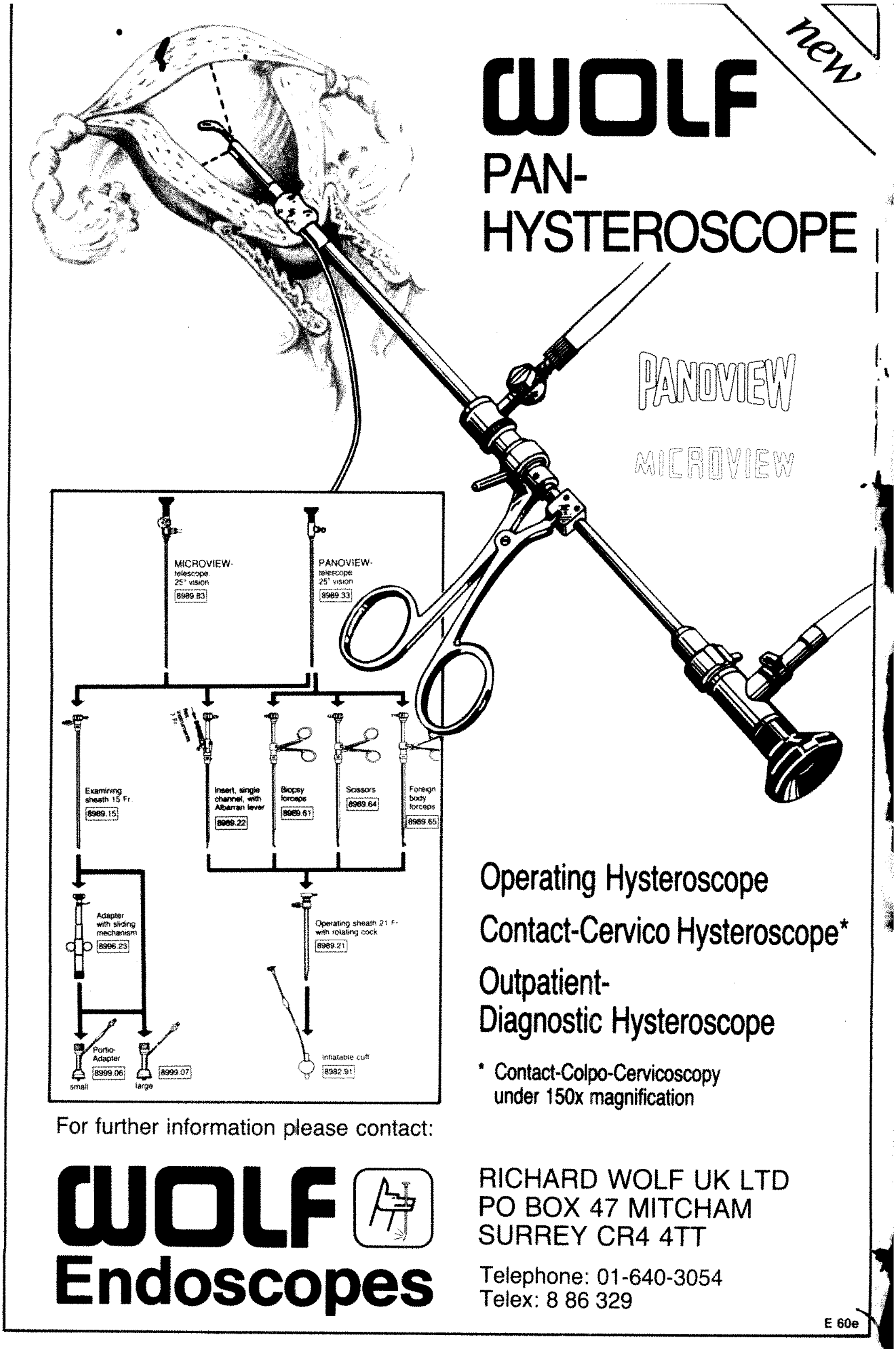

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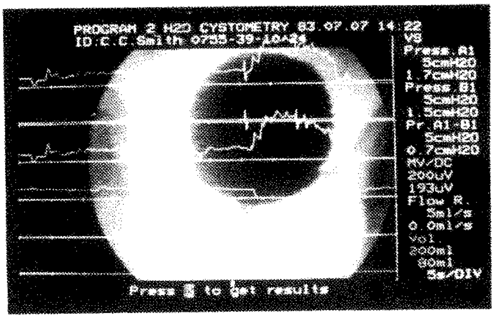

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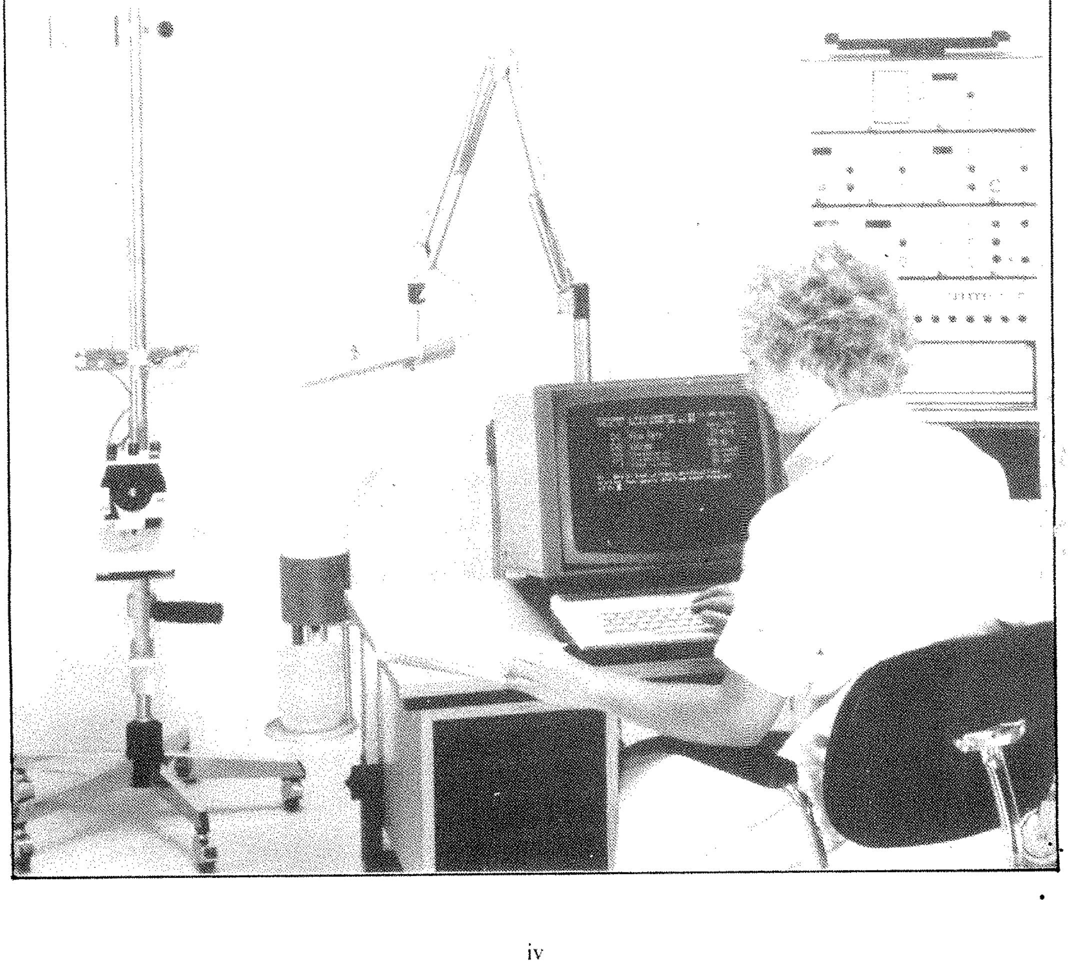

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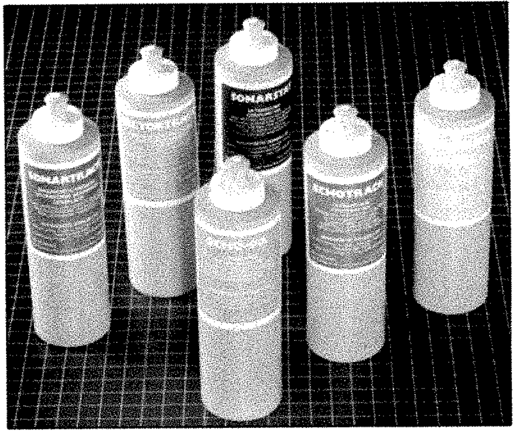

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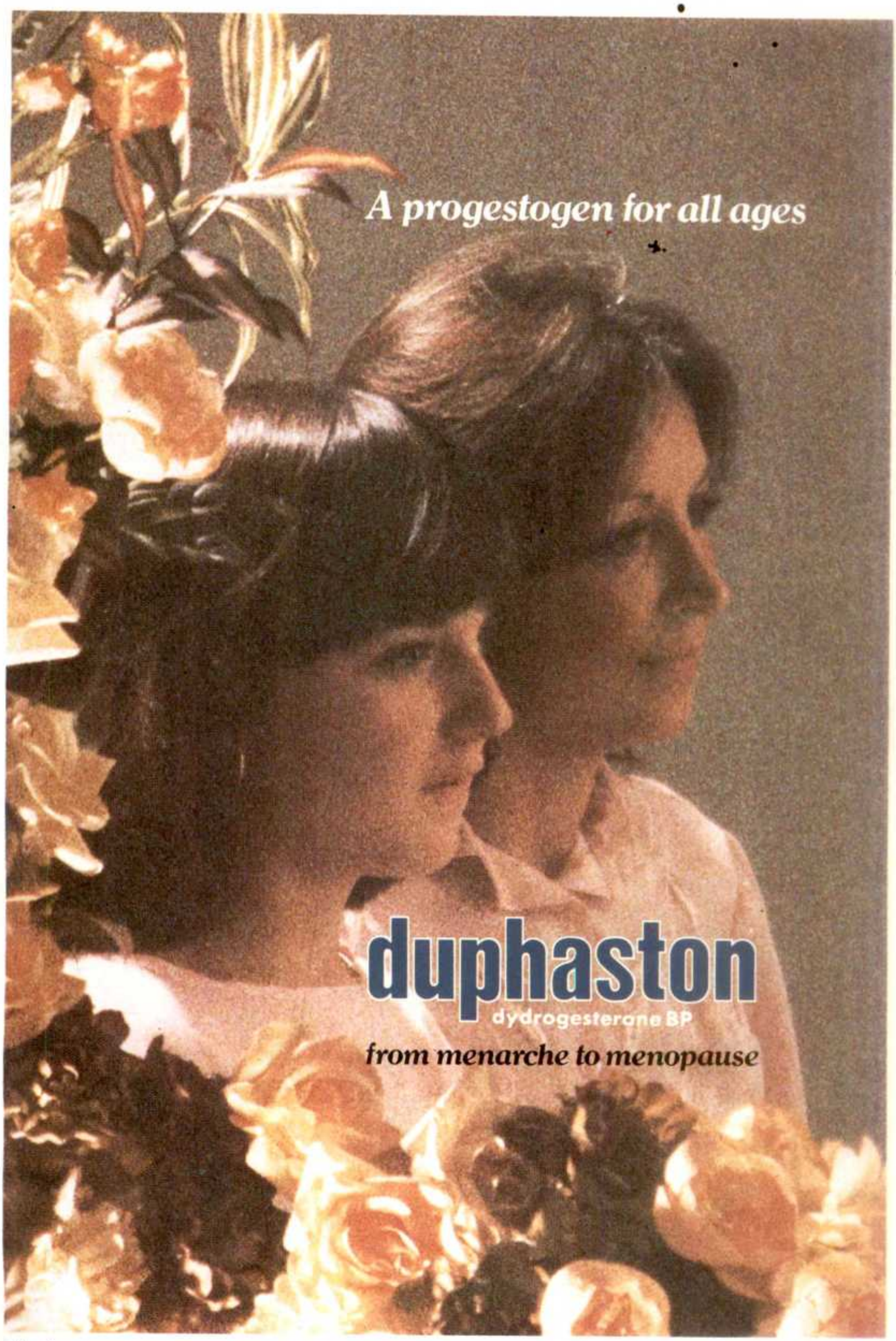

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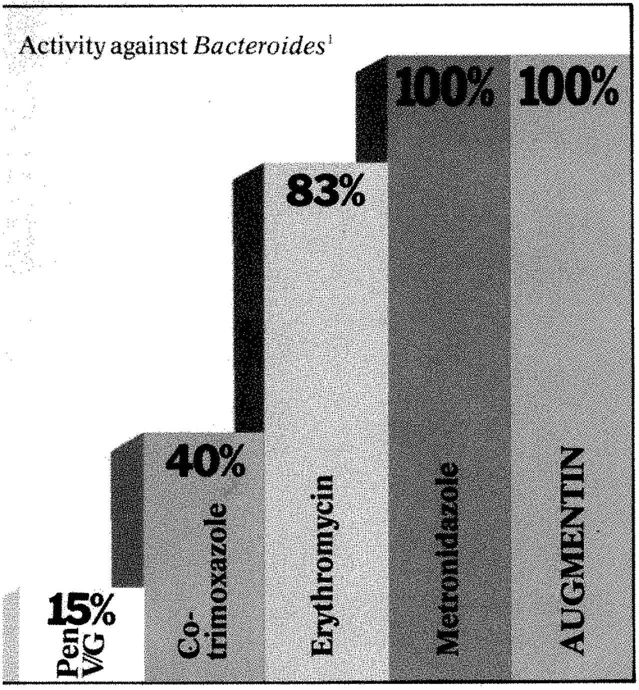

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References: 1. Data published in summary form in: Abbas, A.M.A. et al. Proceedings of the First Augmentin Symposium. Rolinson, G.N. and Watson, A. (eds). Excerpta Medica, 1980, pp 173–183. **2.** Comber, K.R. et al., Ibid, pp 214–219. **3.** Ball, A.P., Mehtar, S. and Watson, A.J. Antimicrob. Chemother (1982), **10**, 67–74. **4.** Ball, A.P., Readings in Infection. Medicine International, 1983. **5.** O'Grady, F., Proceedings of the Second Augmentin Symposium. Leigh, D.A. and Robinson, O.P.W. (eds). Excerpta Medica, 1981, p 244

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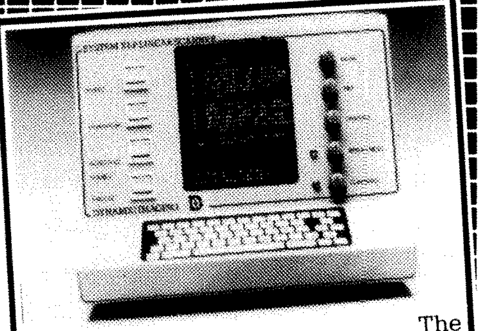

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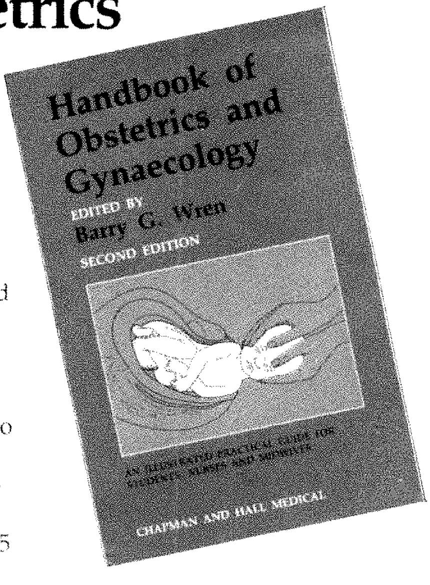
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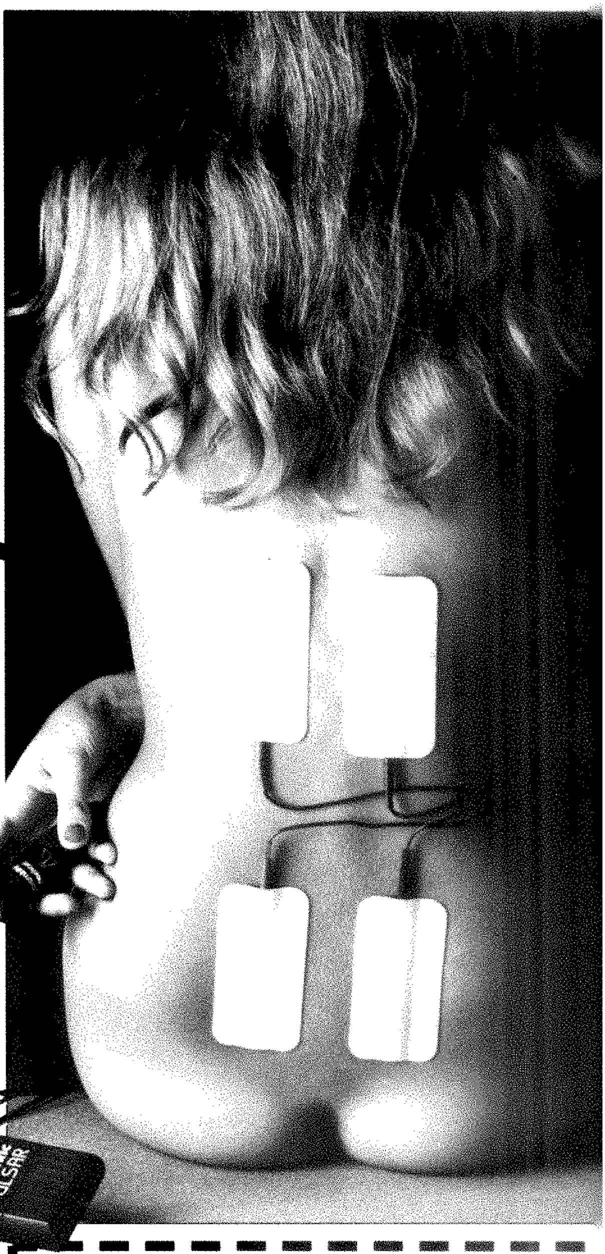

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(1) Stewart, P. — Anaesthesia 34 (1979) 361-364
(2) Tawfik et al — Schmerz, 2 (1982) 98-105
(3) Robson, J. — Anaesthesia 34 (1979) 357-360
(4) Bundsen et al — Acta Obstet Gynecol Scand, 60 (1981) 459-468
(5) Augustinsson et al — Pain 4 (1977) 59-65

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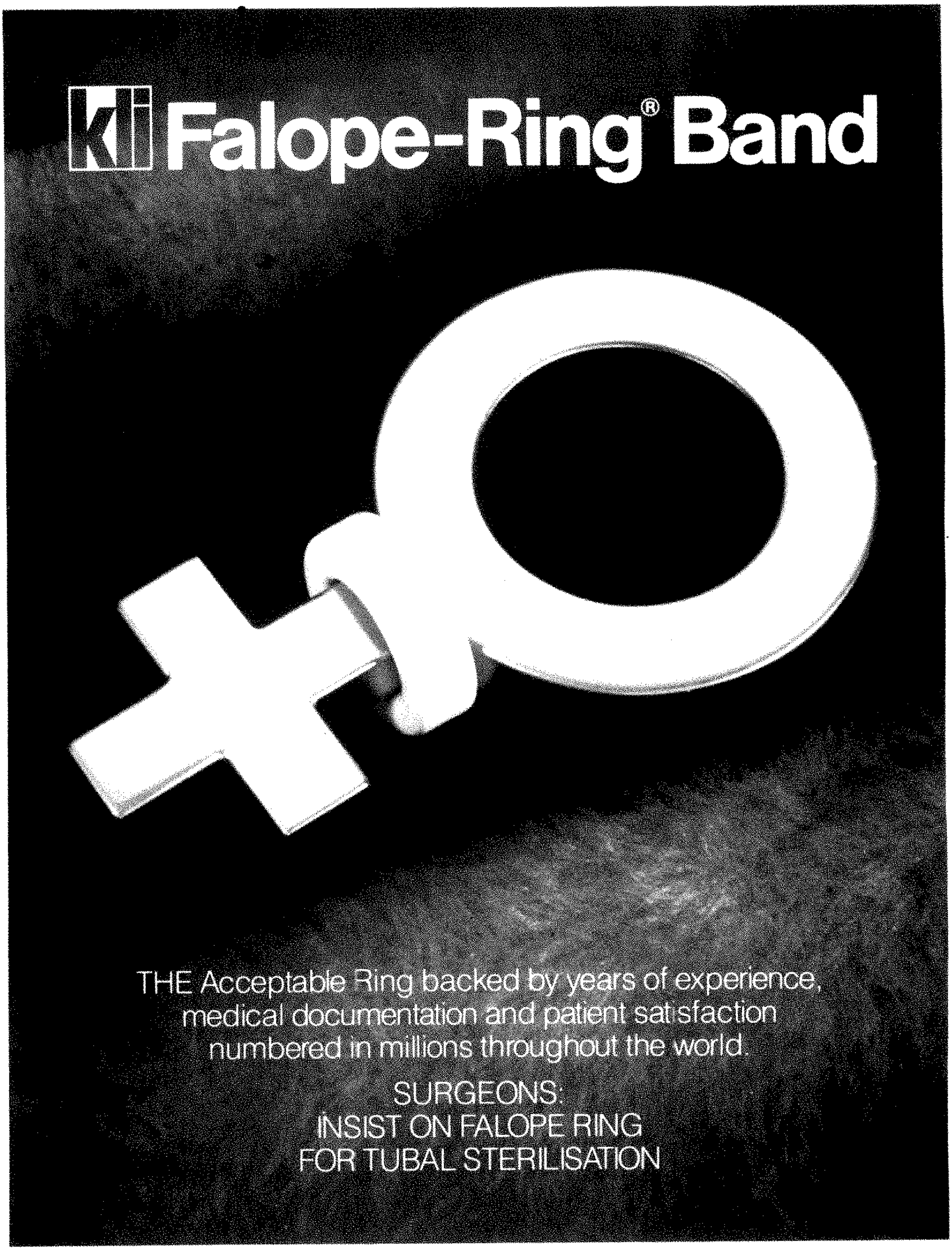

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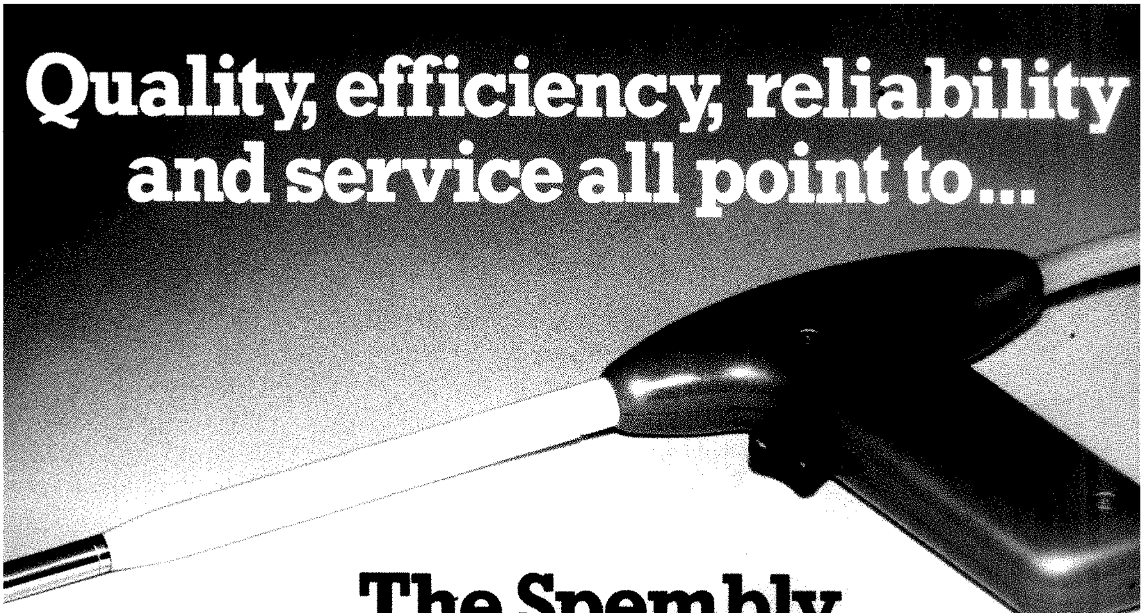

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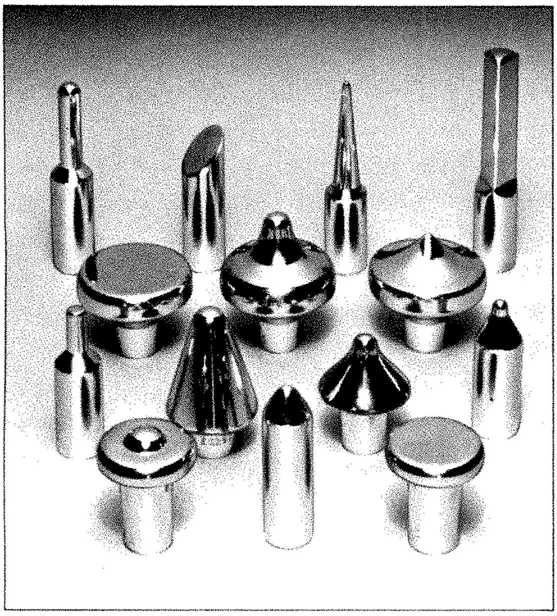

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COMMENTARY

Normal maternity care: whose responsibility?

Midwives are qualified to provide care throughout pregnancy, labour and the puerperium on their own responsibility and to recognize those deviations from the normal that require referral to medical staff for advice and treatment. Data from a recently published report of a national survey of midwives and other health professionals (Robinson *et al.* 1983) demonstrate that although midwives are responsible for much of the care provided for childbearing women, a substantial proportion are not required to exercise fully the degree of clinical responsibility for which they are trained. This is primarily due to the increasing involvement of medical staff in the management of normal maternity care and a consequent restriction of the midwife's responsibilities.

The survey was commissioned and funded by the Department of Health and Social Security. Questionnaires were sent to staff in 60 health districts, randomly selected from all the Regional Health Authorities of England and from Wales. The sample included all the midwives and medical staff in obstetrics in each of the districts, one in three of the general practitioners on the obstetric list and one in two of the health visitors; 4248 midwives, 333 medical staff in obstetrics, 1232 general practitioners and 1177 health visitors returned their questionnaires, representing response rates of 78%, 55%, 67% and 89% respectively. The low response rate for medical staff in obstetrics was primarily due to a poor response from senior house officers; data presented are those for consultants, senior registrars and registrars only, 62% of whom responded.

Considering antenatal care first, it has been maintained that in some clinics medical staff are making the overall assessment of pregnancy of all women, and that midwives are used only as receptionists or chaperones or just to test urine and weigh women (Royal College of Midwives 1977; Brain 1979). The survey showed that a substantial majority of the midwives did perform the various tasks involved in normal antenatal care: interviewing the woman and recording her history; clinical procedures to assess the development of the fetus and to screen the woman for hypertension, abnormal weight gain and abnormal constituents in the urine. Even though a midwife carries out these procedures, she may not necessarily be required to take responsibility for the overall decision that pregnancy is progressing normally. In clinics in which this is regarded as the doctor's responsibility, he or she will carry out the abdominal examination even if it has already been carried out by a midwife, as it is when this examination is made, and the results of the routine investigations are known, that the overall assessment of pregnancy is made. Consequently, the midwives in this survey were asked who usually carried out the abdominal examination in the clinic in which they worked. Only a very small proportion (4%) said it was the midwife only; the great majority worked in clinics in which medical staff were responsible for the assessment of pregnancy, in that 33% said the examination was carried out by a doctor only and 57% said it was carried out by a midwife but then repeated by a doctor.

The survey also showed that few other opportunities existed for midwives to make antenatal assessments on their own responsibility. Midwives' clinics were held in 26 of the 71 consultant units included in the survey, but in 19 of these units, only a very small proportion of women attended the midwives' clinic. Two-thirds of the community midwives worked in clinics in which the general practitioner, and not the midwife, was usually responsible for the overall assessment of pregnancy. The majority of community midwives made few home visits for the purpose of antenatal assessments. Overall, the survey demonstrated that the midwife's clinical role in the provision of antenatal care has been substantially eroded.

Data relating to the clinical assessment of women and babies during their postnatal hospital stay also provide evidence of a duplication of responsibilities of midwives and medical staff. Midwives are qualified to assess the condition of the mother and make daily examinations to do so, but the majority of midwives in this survey worked in units in which medical staff also examined normal postnatal women, either once or twice during their stay (55%) or daily (26%). Less than one-fifth (17%) of the midwives said that medical staff only examined these women if referred by a midwife. Over 80% of the midwives worked in units in which medical staff always made the decisions as to whether the woman and baby were fit to go home—decisions which midwives are also qualified to make.

Although the midwife continues to be the most senior person present at the majority of deliveries in this country, medical staff have become increasingly involved in decision-making about the management of labour and delivery. Many of the midwives in this study worked in units in which certain decisions basic to the management of a normal labour were not made by the midwife caring for the woman, but were made by medical staff or determined by unit policy. For example, less than half of the midwives said that the decision as to when to carry out vaginal examinations was made by the midwife (47%) and the corresponding figure for deciding when to rupture the membranes was 56%. The midwife's responsibilities are affected if decisions concerning the management of normal labour are determined by medical staff or by unit policies (whether formulated by medical staff alone or by medical staff in consultation with senior midwives). Firstly, she is required to follow a pre-determined course of action, whether or not she considers it the most appropriate way to manage a particular case. Secondly, opportunities for midwives to maintain confidence in their ability to make decisions concerning the management of labour are limited, as are opportunities for student and newly qualified midwives to develop this confidence.

Data obtained from obstetric medical staff showed that they were significantly less likely than the midwives to indicate that *midwives* were responsible for the management of normal labour. Of the doctors 46% said that in their labour ward normal women were managed entirely by a midwife unless a problem arose, whereas 80% of the midwives said that this was the case. Although 33% of the medical staff said the midwife decided when to carry out vaginal examinations and 30% said the midwife decided when to rupture membranes, the corresponding figures obtained from the midwives themselves were 47% and 56%. It was not possible to ascertain whether the perceptions of the medical staff were more or less accurate than those of the midwives. Did those doctors who did not perceive midwives as managing normal labour think that this was appropriate? How much responsibility do they think that midwives should have for the management of normal labour?

There is no dispute that it is the obstetrician who should be responsible for women with medical or obstetric complications. There is, however, a lack of consensus over the appropriate division of responsibility between obstetricians and midwives for the care of women who have a normal pregnancy, labour and puerperium. Our study demonstrated a wide variation in the degree of responsibility exercised by midwives. Some were able to use their skills and judgement to the full, referring to medical staff only in the event of an emergency. Others worked in units in which they did not exercise their clinical skills to the full, as medical staff made the overall assessment of pregnancy and made decisions concerning the management of normal intrapartum and postpartum care. If maternity care was provided in a way which allowed all midwives to fulfil the role for which they are trained, then midwifery skills and knowledge gained during training and subsequent experience would not be wasted. At the same time, medical staff would not need to be involved in normal maternity care to the extent that many are at present and could use more of their time on women with medical or obstetric complications. The different ways in which responsibility for maternity care is divided between midwives and medical staff need to be assessed in terms of perinatal outcome and the efficient use of manpower and training resources. Only then can we decide how the skills of different health professionals are best deployed to meet the needs of childbearing women.

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Premalignant lesions and microinvasive carcinoma of the cervix in Jewish women: an epidemiological study

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Summary. During the years 1979–1982 cervical smears were taken from 3974 women at the cervical pathology unit at the Serlin Maternity Hospital, Tel Aviv Medical Center, Tel Aviv. There were 69 patients with positive cytology who had colposcopic directed biopsies which revealed cervical intraepithelial neoplasia (CIN) or a microinvasive lesion; a prevalence rate of 17 per 1000. Epidemiological characteristics of the 69 patients with CIN and microinvasion revealed that these women were younger than those with negative cytology, had more sexual partners and pregnancies, started their sexual activities earlier, and only half of them were married. In the whole series 57% of the women were of Ashkenazi origin and 43% were of Eastern and Sephardic origin, whereas in the group with positive cytology the proportion of women of Eastern and Sephardic origin was twice that of Ashkenazi origin, 64 and 36%, respectively. Only 4·5% of women in the CIN group declared themselves as religiously observant compared with 9 8% in the control group.

Squamous cell carcinoma of the cervix in Jewish women has a low prevalence compared with that in non-Jewish women (Stewart *et al.* 1966). The incidence of preclinical disease, cervical intraepithelial neoplasia (CIN) and microinvasion among Jewish women is difficult to assess as no screening report has yet been published. However, recently we reported a rate of 4·6% for these lesions in a small generally healthy population undergoing screening for the first time (Schachter *et al.* 1981) and 17% in a symptomatic group of women (Baram & Schachter 1982).

Following this initial report a larger study was conducted to determine the prevalence and the epidemiological characteristics of Jewish women in the greater Tel Aviv area with CIN and microinvasion.

Subjects and methods

Between the years 1979 and 1982 nearly 8000 patients were referred for a variety of obstetric and gynaecological complaints to the general out-patient clinic of the Serlin Maternity Hospital, Tel Aviv Medical Center, Tel Aviv. Of these, 3974 patients agreed to attend the cervical pathology clinic which opened early in 1979 for cervical smears and colposcopic examinations. The reasons for referral to the general out-patient clinic by the general physician are listed in Table 1. The patients were classified into two main groups: symptomatic—those who had symptoms which could be attributed to cervical disease, and asymptomatic—those whose referral symptoms had no direct relation to the cervix. Lately there

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Table 1. Reasons for referral in 3974 patients

Reason for referral	No.	%
Symptomatic patients		
Cervical polyp	89	2 2
Post-coital bleeding	278	6 9
Vaginal discharge	1899	47 1
Asymptomatic patients		
Check-up; contraception	348	8 7
Infertility	392	9 8
No symptoms	968	24 3

has been a growing tendency for patients to ask for cervical smear examination only. All the cytological assessments were made by a cytotechnician and were reviewed by the same cytopathologist in the gynecological cytology unit at the Beilinson Medical Center, Petah Tiqva.

Before the women attended the cervical pathology clinic a confidential questionnaire was filled out by a staff member who interviewed the women about their place of birth (or of their parents for those born in Israel), marital status, age at first intercourse, gravidity, number of sexual partners, and religious observance. The women were divided into three main groups according to their (or their parents) place of birth: Eastern—those from North Africa and Middle East countries; Sephardic—the Balkan countries, Turkey, Italy, Spain and South America; and Ashkenazi—Middle and West Europe, North America, South Africa and Australia. As 96% of our patients were born in Israel, we considered their origin according to their parents place of birth. Criteria for religious observance was the woman's declaration of observing religious laws including those relating to sexual behaviour, and family purity such as *Niddah* which involves the abstinence from sexual activity for 7 days after cessation of the menstrual period. On the first visit, in addition to answering the questionnaire the patients had a cervical smear and a gynaecological examination. A cytological report was available by the time of the second visit when all patients had a colposcopic examination. Those with normal cytologic and colposcopic findings were referred back to the general out-patient clinic or to their physicians. Women with a normal cytology and colposcopic findings but with symptoms such as persistent vaginal discharge or postcoital bleeding with cervical 'erosion' were treated by cryosurgery or laser evaporation (Townsend & Ostergard 1971). All had a follow-up examination 2 months later and again, annually. Patients with a positive smear had colposcopically directed biopsies taken of any atypical epithelium. According to the histological report, treatment with cryosurgery, laser or surgical therapy was applied (Wright & Davies 1981; Singer & Walker 1982).

The statistical evaluation was done according to the normal test for proportion (Z) as described by Brownlee (1961).

Results

The cervical smear results are listed in Table 2. Sixty-nine patients had positive smears (17/1000) confirmed by histological examination of colposcopic directed biopsies; seven had signs of warty changes. In 13 patients the cytology reports were considered as false-positive as no colposcopic and histological confirmation for the positive smears were obtained (0 3%). In 94 patients (2·3%) cytological reports were insufficient because of technically inadequate smears.

Table 2. Results of cervical smear in 3974 patients

Cervical smear report	No.	%
Normal	3798	95 7
CIN	69	1 7
False-positive	13	0 3
Technically inadequate	94	2 3

Age distribution of the whole series ranged from 15 5 up to 73 years (Table 3). Of the women with positive smears 55% were aged between 20 and 29 years and a further 35% were between 30 and 39 years of age. The youngest patient with positive cytology was 17 years old and the oldest was 41 years.

The epidemiological characteristics are presented in Table 4. The study group of 69 patients with CIN and microinvasion were compared with those who had negative smears (the control group). The women in the study group were significantly younger than those in the control group; 28·7 and 34 8 years respectively ($P<0·001$). The Jewish population of Israel comprises 40% of Ashkenazi and 60% of Eastern and Sephardic origins. That ratio was reversed in our series with the Ashkenazi population closer to 57% and Eastern and Sephardic only 43%. In spite of that, in the study group of 69 patients, the Eastern and Sephardic women predominated and

Table 3. Age distribution of 3905 patients with negative smears and 69 patients with positive smears

Age (years)	Positive smear (n=69) No	%	% of total series	Negative smear (n=3905) No.	%
15–19	6	8·7	0·1	58	1·5
20–29	38	55·1	0·9	1731	44·3
30–39	24	34·8	0·6	1194	30·6
40–49	1	1·4	0·02	525	13·4
50–59				277	7·1
60–69				97	2·5
≥70				23	0·6

Table 4. Epidemiological characteristics of 69 women with positive cytology and a control group of women with negative cytology

	Positive smear (study group) (n=69)	Negative smear (control group) (n=3905)	P
Origin			
Ashkenazi	25 (36·3)	2214 (56·6)	
Eastern and Sephardic	44 (63·7)	1691 (43·4)	
Marital status			
Single	15 (21·7)	515 (13·1)	<0·001
Married	35 (50·7)	2799 (71·6)	<0·001
Divorced	13 (18·8)	394 (10·1)	<0·11
Widowed	6 (8·6)	197 (5·2)	<0·255
Religious observant	3 (4·3)	385 (9·8)	<0·001
Mean age (years)	28·7	34·8	
Mean age at first intercourse (years)	18·2 (1·4)	23·6 (0·8)	<0·001
Mean age at first pregnancy (years)	20·4 (1·3)	25·3 (1·9)	<0·001
Mean no. of pregnancies	6·1 (1·1)	3·9 (1·4)	<0·001
Mean no. of partners	8·5 (1·5)	4·7 (1·7)	<0·003

Results are numbers of patients with percentages in parentheses or mean (SD) as appropriate.

constituted 64% of this group ($P<0{\cdot}001$). There were significantly more single and fewer married women in the study group compared with the control group. The pattern changed when the proportion of divorcees and widows were compared in the two groups with no statistical difference ($P<0{\cdot}11$ and $P<0{\cdot}255$ respectively). There was a significant difference between the study and the control groups in all the following variables: age at first intercourse, age at first pregnancy, gravidity, and number of sexual partners, with P values between 0·001 and 0·003.

Only three patients in the study group (4·3%) declared adherence to religious observance compared with 9·8% in the control group, a significant difference ($P<0{\cdot}001$). We tend to accept the woman's declaration on religious observance as reliable, since it agrees with the 14% of orthodox Jews in the general Jewish population in Israel.

Discussion

As cervical smears are not routinely performed in Israel, results of a screening study on CIN and microinvasion and its prevalence cannot be obtained. The reason for that is the belief that squamous cell carcinoma of the cervix is not common amongst Jewish women and therefore the cost benefit of screening is unjustified.

Knowing the epidemiological factors relating to the aetiology of the disease, i.e. low socioeconomic class and sexual promiscuity, it was difficult for us to accept that concept for two main reasons: (i) previous reports (Stewart *et al.* 1966; Pridan & Lilienfeld 1971; Menczer *et al.*

1978) dealt with clinical disease only; they were not prospective but retrospective studies based on archive records; (ii) the Jewish population reviewed in those reports was believed to possess a much stricter code of sexual behaviour, compared with the present reputedly more promiscuous Israeli younger generation. The epidemiological characteristics of the women with CIN and microinvasion show that they were younger and more sexually active than the control subjects, they had more pregnancies and sexual partners and fewer of them considered themselves as religiously observant. Pridan & Lilienfeld (1971) reported a higher percentage of women with clinical disease born in Europe (40 2%) than in North Africa (36 7%). In a series of 532 Jewish women with invasive disease, Menczer *et al.* (1978) reported a significantly higher prevalence among the North African and Asian born Israeli women, 9 4 per 100 000, compared with 2 9 per 100 000 among the European born Israeli women. The findings are compatible with our study as the prevalence of preclinical and microinvasive disease was higher among the Eastern and Sephardic women (44 out of 1735, 2 5%) (North African and Asian in Pridan's and Menczer's studies) than among the Ashkenazi women (25 out of 2239, 1·1%) (European women in Pridan's and Menczer's studies). Two points arise from this finding, first, that Ashkenazi women have a higher awareness of the early detection facilities, as they comprise only 40% of the population but almost 60% of the clinic attenders; second, that the Eastern and Sephardic ethnic groups have a higher risk of developing preclinical and clinical disease with a lower awareness of the early detection facilities.

We expected to find positive smears in our series, but the prevalence of 17/1000 was somehow surprising as it was not much lower than that reported by Soost *et al.* (1982), 26/1000, in a first mass screening examination of non-Jewish women in the Federal Republic of Germany. It is true that we were dealing with a selective and unscreened population which might explain the relatively high prevalence, but only the patients with post-coital bleeding (7%) can be considered symptomatic in respect of cervical disease (Table 1). The other 93% can be classified as non-symptomatic for cervical pathology as their reasons for referral were very general and were not indicative of preclinical or clinical disease. Similarly in a series of 305 Jewish patients selectively referred for cervical examination, Menczer *et al.* (1982) reported a prevalence of 26/1000 for CIN and microinvasive disease. Schachter *et al.* (1981) in a preliminary report of nearly 20 000 screening examinations of Jewish women in Israel reported the prevalence of 1 9/1000 for CIN and microinvasive disease.

We have shown that the preclinical stage of squamous cell carcinoma of the cervix among Jewish women in Israel is not rare. The question which arises and should be answered is—why is the incidence of clinical disease relatively low among Jewish women in Israel; about 60 new cases per year (Steinitz & Costin 1970). In a series of 250 Jewish women who underwent hysterectomy or cervical biopsy for a variety of reasons apart from malignancy of the cervix, Czernobilsky *et al.* (1977) reported a prevalence of 44/1000 of dysplastic lesions of varying severity. The authors suggested that in most Jewish women the histological spectrum leading to carcinoma inexplicably stops at the dysplastic stage, or that dysplasia may represent a non-specific reaction and not necessarily a stage in the process leading to carcinoma. It is suggested that only a small proportion of patients with CIN 1–2 will develop invasive disease; (Thomas 1973; Thomas & Anderson 1974), while some 20–30% of CIN 3 will progress.

As long as a prospective screening study cannot be conducted in Israel, the accurate incidence of CIN and the development rate of the clinical disease from it will remain obscure. Moreover, as the disease relates to sexual promiscuity, and we believe that there is practically no difference between the sexual behaviour of the young Israeli generation and that of Western Europe and the USA, it seems possible that unless protective measures are taken (screening especially high-risk groups) it is only a question of time before cervical cancer becomes a common disease in Israel.

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A routine system for monitoring perinatal deaths in Scotland

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Summary. Since 1983 the monitoring of perinatal deaths in Scotland has been incorporated into the established data collection system which monitors maternal and child health in Scotland. This paper describes the transition from a research project to the routine system and the extension of the data collection to include paediatric and pathological findings. This information is provided by local co-ordinators in active clinical practice. Baseline data are obtained from the routine maternity discharge document (SMR 2). A summary of the findings for the first 4 years of the study, 1977, 1979, 1980 and 1981 is presented, including information about birthweight and gestation-specific perinatal mortality rates; perinatal mortality rates by time of death in relation to labour and singleton and multiple perinatal mortality rates by the obstetric complication preceding the death.

The perinatal mortality rate was first recorded in Scotland in 1939 and since that time it has fallen steadily from 68/1000 to 12/1000 total births in 1981 (Registrar General Scotland 1981). Despite this continuing trend, which had occurred throughout the United Kingdom, concern was expressed about unacceptably high rates which culminated in an investigation by the House of Commons Social Services Committee (1980). A greater understanding of the events leading up to each death was required. In order to determine the obstetric events preceding each death, a survey of all perinatal deaths occurring in Scotland during 1977 was undertaken as a research project.

This paper describes the development of the research project from a review of perinatal deaths occurring in 1 year to a routine system for monitoring perinatal deaths, presents a summary of the findings of the first 4 years studied—1977, 1979, 1980 and 1981—and describes how perinatal mortality in Scotland will be monitored in the future.

Research project to routine system

The first Scottish study of perinatal deaths was undertaken by a research team carrying out a retrospective case record review of each death. The chairman of each obstetric division and each community medicine specialist responsible for maternity services were contacted personally about the study by the senior member of the research team. All obstetricians in Scotland (115 in 1977) agreed to allow members of the research team access to the relevant case records. Information about the occurrence of a stillbirth or first week death was obtained from the Registrar General (Scotland).

The results of that study were analysed the following year and made available to each division of obstetrics (McIlwaine *et al.* 1979). The

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second phase, designed to develop an ongoing system, also funded by the Scottish Chief Organisation, was carried out between 1979 and 1982. In this phase, one obstetrician in nearly every hospital undertook to provide the data when requested for all perinatal deaths in that hospital or in the whole Health Board. Initially some of the information was still collected directly from the case records by members of the research team but by 1982, all but two hospitals in Scotland were providing their own information. In one health board area the data collection was organized by a community medicine specialist, in all others the organizer was a consultant obstetrician. The requests, organized by the research secretary, were triggered by the stillbirth or death certificates received regularly from the Registrar General (Scotland).

During the 4 years studied (1977, 1979, 1980 and 1981) 270 581 babies were born in Scotland, 3840 of whom died during the perinatal period, giving a perinatal mortality rate of 14/1000 total births. This figure represents a reduction in the perinatal mortality rate from 18/1000 total births in 1977, to 12/1000 total births in 1981, a reduction which occurred in all health boards and for all causes of death. Since 1970 Scotland has had baseline information about all births on a standard maternity discharge document (SMR 2) (Cole 1980). From these data and the research information it is therefore possible to present details of perinatal deaths by the obstetric event leading to death in both singleton and multiple pregnancies (Table 1); by birthweight and gestation length in infants (excluding lethal malformations) (Table 2); by time of death in relation to labour in both singleton and multiple perinatal deaths (Table 3); and by time of death in relation to labour in different birthweight groupings (Table 4). Many other analyses have been undertaken and have been presented in a research report (McIlwaine *et al.* 1984).

The research phase of the project ended in the spring of 1983, but it was felt that the method of data collection and the presentation of annual reports should continue. The monitoring of perinatal deaths has now become incorporated into the established data collection system which monitors maternal and child health in Scotland. A research secretary (F.D.) is co-ordinating the transition from research project to routine system during the next 2 years, thereafter the responsibility for monitoring perinatal deaths in Scotland will be wholly absorbed by the staff of the Information Services Division of the Common Services Agency of the Scottish Home and Health Department.

The Chief Medical Officer for Scotland (*British Medical Journal* 1982) set up a Perinatal Mortality Review Advisory Group which would report directly to him and: advise him on the collection of data for epidemiological monitoring

Table 1. Perinatal deaths by obstetric classification[a]

	Singleton births		Multiple births		Total births	
	No.	Rate/ 1000	No.	Rate/ 1000	No.	Rate/ 1000
Unexplained death						
Low birthweight (<2500 g)	1021	3·8	243	48·3***	1264	4·7
Normal birthweight (≥2500 g)	399	1·5	6	1·2	405	1·5
Antepartum haemorrhage	435	1·6	23	4·6***	458	1·7
Toxaemia	297	1·1	20	4·0***	317	1·2
Trauma	129	0·5	8	1·6	137	0·5
Maternal disease	145	0·5	12	2·4*	157	0·6
Rhesus disease	47	0·2	2	0·4	49	0·2
Other	80	0·3	2	0·4	82	0·3
Total (excluding deformity)	2553	9·6	316	62·8	2869	10·6
Fetal deformity	864	3·3	48	9·5***	912	3·4
Grand total	3417	12·9	364	72·3	3781	14·0

Significance of differences * $P<0{\cdot}05$; ** $P<0{\cdot}01$; *** $P<0{\cdot}001$.

[a] The aim of the classification devised by Baird *et al.* (1954) is to classify each death according to the factor which seemed most likely to initiate the train of events resulting in the death.

Table 2. Birthweight and gestation-specific perinatal mortality rates in singleton infants (excluding deaths from fetal deformity)

	Birthweight					
Gestation (weeks)	<1000 g	1000–1499 g	1500–1999 g	2000–2499 g	⩾2500 g	Total[a]
<28	913 (252)	493 (75)	(3)	—	(1)	621 (344)
28–31	777 (167)	403 (311)	205 (107)	165 (16)	(7)	353 (622)
32–36	603 (47)	325 (156)	129 (210)	49 (181)	22 (118)	65 (727)
37–39	(1)	(9)	102 (46)	23 (99)	4 (345)	6 (502)
40–41	(0)	(2)	(4)	10 (22)	2 (252)	2 (283)
⩾42	(2)	(1)	(3)	(3)	5 (42)	8 (68)
Total[a]	784 (469)	370 (554)	135 (373)	30 (321)	3 (765)	10 (2553)

Numbers in brackets.

[a] Totals include 71 cases where either birthweight and/or gestation length were not known.

Table 3. Perinatal mortality rates per 1000 singleton and multiple births by time of death in relation to labour

	Singleton	Multiple	Total
Normally formed			
Antepartum	4 (1128)	14 (71)	4 (1199)
Intrapartum	1 (319)	6 (28)	1 (347)
Postpartum	4 (1078)	43 (217)	5 (1295)
Abnormally formed			
Antepartum	1 (146)	1 (7)	1 (153)
Intrapartum	1 (176)	2 (11)	1 (187)
Postpartum	2 (537)	6 (30)	2 (567)
Total			
Antepartum	5 (1274)	16 (78)	5 (1352)
Intrapartum	2 (495)	8 (39)	2 (534)
Postpartum	6 (1615)	49 (247)	7 (1862)

Numbers in brackets.

of perinatally related deaths and related topics; advise on the interpretation of these data and on the implications for the organization and development of these services; prepare regular reports; undertake occasional studies on smaller groups of special interest and identify areas where further research is needed; provide feed-back of information to local groups of clinicians and encourage and assist with the development of their local perinatal audit procedures; and finally, co-operate, when appropriate, with other national surveys and enquiries concerned with perintal and infant deaths in Scotland and elsewhere.

Although the initial survey had been carried out by obstetricians and had provided information about the obstetric events leading up to the death of the baby, it was obvious that a more detailed picture of the events prior to death was required. The original classification devised by Baird *et al.* (1954) required to be extended to include information about paediatric events and pathological findings, and therefore the group appointed by the chief medical officer included members representing community medicine, general practice, obstetrics, paediatrics and pathology.

Scotland has not adopted the proposals of the Working Party on Confidential Enquiries, which followed the Royal College of Obstetricians and Gynaecologists Working Party on Perinatal Audit and Surveillance (RCOG 1980) suggesting the establishment of local panels at area health board level, and the appointment of two regional assessors. The composition of the Perinatal Mortality Review Advisory Group, however, is very similar to the proposed regional perinatal review group.

Current developments and future plans

In order to obtain paediatric information, pilot

Table 4. Perinatal mortality rates per 1000 singleton and multiple births by time of death in relation to labour by birthweight (excluding deaths from fetal deformity)

Birthweight (g)	Singletons	Multiples	Total
<1000			
Antepartum	204 (122)	92 (12)	184 (134)
Intrapartum	50 (30)	38 (5)	48 (35)
Postpartum	525 (314)	786 (103)	572 (417)
1000–1499			
Antepartum	142 (213)	53 (17)	126 (230)
Intrapartum	19 (28)	25 (8)	20 (36)
Postpartum	208 (312)	234 (75)	213 (387)
1500–1999			
Antepartum	65 (180)	19 (13)	56 (193)
Intrapartum	14 (39)	10 (7)	13 (46)
Postpartum	54 (150)	27 (18)	49 (168)
2000–2499			
Antepartum	19 (203)	13 (17)	18 (220)
Intrapartum	4 (45)	3 (4)	4 (49)
Postpartum	6 (68)	4 (6)	6 (74)
⩾2500			
Antepartum	2 (395)	2 (5)	2 (400)
Intrapartum	1 (172)	2 (4)	1 (176)
Postpartum	1 (195)	3 (8)	1 (203)
Total			
Antepartum	4 (1113)	13 (64)	4 (1177)
Intrapartum	1 (314)	6 (28)	1 (342)
Postpartum	4 (1039)	43 (210)	5 (1249)
	(2553)*	(316)†	(2869)

Numbers in brackets.

* Includes 87 cases where birthweight or time of death in relation to labour was not given.

† Includes 14 cases where birthweight or time of death in relation to labour was not given.

studies of two perinatal death forms are being undertaken in Scotland during 1984. The guidelines laid down for clinicians are the same as those used in the Northern Region's perinatal survey (Hey, personal communication). It is also envisaged that information will be supplied by the pathologist. To this end Scottish neonatal pathologists are working together to produce guidelines for post-mortem examination. The information thus obtained will provide a comprehensive picture of the circumstances associated with each perinatal death.

The two areas where improvement in the perinatal mortality rate may most obviously be sought are in multiple pregnancies, and in the normally formed very-low-birthweight infant. Two studies are currently in progress to investigate these problems, a retrospective case record review of the obstetric management and outcome of twin pregnancies delivered in Scotland during 1983, and all babies born during 1984 weighing <1750 g are being studied by neonatal paediatricians from the antenatal period until they reach 2 years of age. Attempts are also being made by the Perinatal Mortality Review Advisory Group to further quantify reproductive loss by asking hospitals to provide the research secretary with details of spontaneous abortions from 20 to 27 weeks gestation. The next stage will be to seek a method of collecting, routinely, information of perinatally related deaths which occur after the first week of life.

We believe that this model, using routinely collected denominator information (SMR 2) with additional information about each death provided by the clinicians, is an appropriate way to monitor perinatal deaths, and it is in this way that the review of perinatal mortality in Scotland will continue in the future.

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Controlled trial of external cephalic version

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Summary. A prospective randomized, controlled trial involving 640 singleton breech presentations after 30 weeks gestation was conducted to assess the value of external cephalic version. In 310 patients external cephalic version was attempted; the other 330 patients in whom version was not attempted constituted a control group. There were three perinatal deaths directly attributable to external cephalic version. No significant differences were found between the study and control groups respecting the incidence of vaginal breech delivery, caesarean section rate, perinatal mortality and morbidity. Our results suggest that there is no place for external cephalic version before 36 weeks gestation.

Breech presentation and delivery are associated with a high perinatal mortality and morbidity. Even when congenital malformations and intrauterine deaths are excluded, the perinatal mortality after breech delivery is three to four times higher than that associated with vertex delivery (Rovinsky *et al.* 1973). One study of breech presentations found that 10% of the vaginal breech births had low Apgar scores (<7 at 5 min) compared with only 2% of those born by caesarean section (Collea *et al.* 1978). The British Births Survey (Chamberlain *et al.* 1975) found that after breech delivery 14% of the newborn infants developed breathing difficulty compared with 3% after a vertex delivery. Intracranial damage at autopsy was found in a higher proportion of infants born by the breech compared with those born by the vertex (Wigglesworth & Husmeyer 1977). The correct management of breech presentation is controversial. Attempts to reduce fetal hazards inherent in a vaginal breech delivery have resulted in an unacceptably high caesarean section rate, which has approached 100% in some centres.

Green *et al.* (1982) reported that the caesarean section rate for term breech delivery in their hospital had increased from 22% in 1963 to 94% in 1979. Advocates of external cephalic version maintain that this simple procedure reduces the occurrence of breech presentation thereby diminishing the caesarean section rate, perinatal mortality and morbidity (Hibbard & Schumann 1973; Ranney 1973). On the other hand Hay (1959) reported a similar incidence of breech delivery between units which practised external cephalic version and those which did not. In a prospective randomized controlled trial Hofmeyr (1983) demonstrated convincing success where external cephalic version was performed after the 36th week of pregnancy.

Most of the publications on the benefits of external cephalic version, however, have been retrospective and uncontrolled. The present study was designed to assess the impact of external cephalic version using a randomized prospective trial, where gestation was less than 36 weeks.

Patients and methods

All the patients were attending the Greater Harare unit. The unit consists of a central teaching hospital which supervises antenatal care and deliveries in 10 peripheral clinics situated in the city of Harare. All were of African origin. Patients were referred to the specialists' antenatal clinic from the peripheral clinics. There were four antenatal clinics per week and patients were allocated to a version or non-version group depending on the day they attended. On Mondays and Wednesdays external cephalic version was performed whereas on Tuesdays and Thursdays it was not. Once a patient had been allocated to a group she remained in that group. Patients were excluded from the trial for the following reasons: multiple pregnancy, previous caesarean section, intrauterine death, antepartum haemorrhage, congenital malformations and rhesus isoimmunization.

Study group (version attempted)

This group included 310 consecutive patients with a breech presentation on whom external cephalic version was attempted by consultants. External cephalic version was performed in the antenatal clinic between 33 and 36 weeks gestation. If the first attempt failed, the procedure was repeated up to three times in subsequent visits. No analgesic, anaesthetic or tocolytic agents were used.

Control group (version not attempted)

This group included 330 consecutive patients with breech presentation on whom no version was performed. The patients with persistent breech presentation were assessed by consultants for the method of delivery. This assessment consisted of clinical and radiological estimation of the pelvis and clinical estimation of fetal size. When admitted in labour or for caesarean section the patients were managed by the consultant on call for that day.

The significance of differences in findings between the study and control groups was tested with the χ^2 analysis.

Results

The two groups were similar in age, marital status, social class, parity and ethnic background. The mean birthweight in the study group was 3262 g (SD 360) and in the control group 3170 g (SD 315). The distribution of parity together with the age and height of the patients in the two groups are shown in Table 1.

Table 1. Characteristics of patients with breech presentation in the study and control groups

	Study group ($n = 310$)	Control group ($n = 330$)
Age (years) mean (SD)	24 (4·8)	25 (4·0)
Height (cm) mean (SD)	158 (5·0)	157 (5·3)
Parity *n* (%)		
0	65 (21)	60 (18)
1–3	174 (56)	182 (55)
4–7	71 (23)	88 (27)

Successful external cephalic version

A distinction was made between immediate and final success. The former refers to the group of patients who had a successful external cephalic version in the antenatal clinic on the first or subsequent attempt, but some of them reverted to breech presentation before delivery. The final success group includes those patients who had a successful external cephalic version with the fetus remaining cephalic up to the time of delivery. A total of 220 patients had a successful version at between 33 and 36 weeks; these included 190 of the 245 multiparae (78% success) and 30 of the 65 nulliparae (46% success). A further 30 patients (13 nulliparae and 17 multiparae) had a successful version at between 36 and 40 weeks gestation. The final success rates are shown in Table 2. Out of 250 fetuses who had undergone successful version antenatally only 134 were still cephalic at birth (a final success rate of 43% as opposed to an immediate success rate of 80%). This means that 54% of the successful antenatal versions were born cephalic while 46% reverted to breech presentation. The reversion rate was lower in the nulliparous (16%) than in the parous patients (48%) ($P<0{\cdot}05$).

Table 2. Comparison between successful version at the antenatal clinic and presentation at delivery in the study group

Result of version at antenatal clinic	No. of patients	No. cephalic at delivery
Successful		
at 33–36 weeks	220 (71)	122 (55)
at 36–40 weeks	30 (10)	12 (40)
Failed	60 (19)	14 (23)
Total	310 (100)	148 (48)

Percentages are shown in parentheses.

Failed external cephalic version

There were 60 patients on whom version completely failed; the number of attempts varied from three to five. Of these 37 were parous (15% failure rate) and 23 were nulliparous (35% failure rate). Among the 60 failures, 14 fetuses spontaneously turned to cephalic after 36 weeks (11 parous and three nulliparous patients).

Complication of external cephalic version

There were major complications in three patients resulting in one neonatal and two fetal deaths. Placental abruption occurred in two parous patients within 6 h of version, both were at 36 weeks gestation. The third patient had a premature labour at 33 weeks soon after a version and gave birth to a baby who died of hyaline membrane disease. Another patient with antepartum haemorrhage settled with rest, went to full term and gave birth to a normal infant.

Presentation at the time of delivery

Tables 3 and 4 show the number of vertex and breech deliveries in the study and control groups; there are no significant differences between the two groups. Vertex deliveries occurred in 45% of the study group, comparing favourably with 47% in the control group (χ^2; $P>0·05$). The incidence of breech presentation at delivery was 52% in the study group and 51% in the control group.

Table 3. Mode of delivery

	Study group ($n = 310$) n (%)	Control group ($n = 330$) n (%)
Normal vertex delivery	141 (45)	156 (47)
Assisted breech delivery	116 (37)	120 (36)
Caesarean section (breech)	46 (15)	48 (14)
Caesarean section (cephalic)	5 (2)	4 (1)
Vacuum extraction	2	2

(χ^2; $P>0·05$)

Caesarean section rate

The rates were 16 and 15% in the study and control groups respectively. When the numbers of breech presentation at delivery are considered separately, the caesarean section rate becomes 28% in the study group and 29% in the control group. Table 5 shows that of the caesarean sections for breech presentation there were more emergency sections (45%) in the study group than in the control group (23%). The rates for elective caesarean section were 55% and 77% in the study and control groups respectively ($\chi^2 = 4·37$; $0·001<P<0·005$).

Table 4. Breech presentation at delivery by parity in the study and control groups

	Study group		Control group	
Parity	Total no.	Breech at delivery n (%)	Total no.	Breech at delivery n (%)
0	65	35 (54)	60	33 (55)
1–3	174	82 (47)	182	79 (43)
4–7	71	45 (63)	88	56 (64)
Total	310	162 (52)	330	168 (51)

(χ^2; $P>0·05$).

Table 5. Caesarean section for breech presentation

	Study group n (%)	Control group n (%)
Elective	25 (55)	37 (77)
Emergency	21 (45)	11 (23)
Total	46	48

($\chi^2 = 4·37$; $0·01<P<0·05$)

Fetal outcome

Table 6 shows a summary of morbidity and mortality for both groups. Low Apgar scores (<7 at 5 min) occurred in 3·5% of the study group (nine were born by assisted breech and two were cephalic presentations). None of the babies suffered any permanent neurological damage. Low Apgar scores occurred in 3·6% of the control group (eight out of 12 babies were born by assisted breech, four were cephalic presentations one of whom was born by vacuum extraction). None of the babies had any permanent disability at 6 weeks of age. Two babies in the study group had fractures of femur and clavicle, respectively. They were treated in the neonatal ward and recovered uneventfully.

Table 6. Fetal outcome in the study and control groups

	Study group ($n = 310$)	Control group ($n = 330$)
Low Apgar score (<7 in 5 mins)	11 (3·5%)	12 (3·6%)
Neonatal morbidity	2	0
Intrapartum deaths	4	3
Neonatal deaths	1	2
Perinatal mortality	*8 (2·6%)	5 (1·5%)

* This includes the three perinatal deaths as a result of version.

Intrapartum deaths

There were four intrapartum deaths in the study group and three in the control group. Of the four deaths in the study group only one was associated with a difficult assisted breech delivery. Of the other three deaths, one was due to cord prolapse in a cephalic presentation, another was due to intrapartum anoxia in a cephalic presentation and the third occurred in an infant with Down's syndrome. Of the three deaths in the control group two were due to cord prolapse in vertex presentations and one was due to fetal hypoxia in a patient booked for elective caesarean section who reached the hospital when the breech was half born.

Neonatal deaths

There were three deaths: one was in the study group due to intrapartum anoxia in a vertex presentation and two in the control group one of which was due to a difficult breech delivery and the other was due to congenital heart disease.

Discussion

In the present study breech delivery occurred in 52% of the study group and in 51% of the control group. This similarity of breech delivery between the two groups supports the findings of Hay (1959) who reported similar incidences of breech delivery in units where external cephalic version was practised and in those where it was not. In most studies where external cephalic version was found effective in reducing the occurrence of breech delivery (Hibbard & Schumann 1973; Ranney 1973; Neely 1961), the procedure was carried out under conditions which differed markedly (some versions were done under general anaesthesia and in another study the procedure was started as early as 26 weeks). The varying conditions under which these studies were made and the lack of controls casts doubt on the significance of their findings.

It is important to make a distinction between immediate success with external cephalic version and final success, those who remain cephalic after version until delivery. It is well known that some fetuses spontaneously revert to breech before birth. Vartan (1945) reported the rate of reversion to breech to be 22% and a reversion rate of 11% was reported by Friedlander (1966). In our study the initial success rate for version at 33–36 weeks gestation was 71% (220 out of 310) but only 122 (55%) remained cephalic until delivery. The spontaneous reversion rate for all the 250 fetuses that were turned initially was 46%. The reversion rate in nulliparae was significantly lower (16%) than that in multiparae (43%) ($P<0{\cdot}05$). The high reversion rate in our study could possibly be due to two factors. First, the shape of the African pelvis which keeps the head high until labour is established and, second, the majority of our patients were multiparous with lax abdominal muscles which predispose to unstable lie. On the other hand the fact that the number of patients with cephalic presentation at the time of delivery was similar in the study and control groups suggests that there may be another explanation and supports the hypothesis that these successful external cephalic versions merely anticipate spontaneous versions that would have occurred anyway.

External cephalic version is potentially dangerous to the fetus. Husslein (1965), in a survey of continental obstetric units, found that the perinatal mortality was greater in units where version was routine compared with non-version units. Bradley-Watson (1975) highlighted the dangers of external cephalic version. In the present study there were three perinatal deaths directly attributable to external cephalic version (1·0% mortality rate) in the study group and the perinatal mortality as a result of difficult breech delivery was 0·6% in the control group. There is, therefore, no difference between these two groups. The situation was similar for intrapartum deaths. From the data presented the hazards of external cephalic version exceed the benefit. We believe that version is not a justifiable procedure.

There has been a trend to resort to caesarean section whenever an obstetrician is faced with a breech presentation (Green *et al.* 1982; Quilligan & Zuspan 1982; Pritchard & MacDonald 1980). In this study we wanted to determine whether external cephalic version effectively reduces the caesarean section rate. The caesarean section rate for breech presentation in the study group was 28% and in the control group 29%. There were no fetal or maternal deaths in either group and no statistically significant difference in the prevalence of caesarean section between the two groups ($P>0{\cdot}05$). There was, however, a significant difference between the study and control group in the timing of caesarean section. In the study group there were more caesarean sections performed as emergencies in labour (45%) compared with 23% for the control group ($\chi^2 = 4\cdot37$; $0\cdot01<P<0\cdot05$). This is explained by the fact that fetuses successfully turned to cephalic in the antenatal clinic, and judged suitable for vaginal delivery, spontaneously reverted to breech before the onset of labour and were found unsuitable for breech delivery due to fetopelvic disproportion.

The caesarean section rate in the present study is low compared with other studies (Green *et al.* 1982; Quilligan & Zuspan 1982; Pritchard & MacDonald 1980). This low caesarean section rate shows that careful antenatal assessment, combined with close intrapartum supervision and use of caesarean section when labour is slow allows assisted breech delivery in 72% of all term breech presentations without compromising neonatal outcome. The fact that the caesarean section rate for breech presentation in our control group was low (29%) and the perinatal loss due to assisted breech delivery was only 0·6% supports the view that external cephalic version is unnecessary because the fetal loss due to the procedure (1%) is greater than that due to vaginal breech delivery.

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Spontaneous cephalic version of breech presentation in the last trimester

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Summary. A prospective longitudinal investigation of spontaneous cephalic version from breech presentation in the last trimester is reported. All pregnancies were assessed with ultrasound in the 32nd week of gestation, and were thereafter checked weekly. Of the 310 singleton breech presentations identified at 32 weeks, spontaneous cephalic version occurred in 177 (57%) while breech presentation persisted in 133 patients (43%). Of 140 patients with a breech presentation at delivery 95% were already presenting by the breech in the 32nd week. Spontaneous cephalic version was less likely in pregnancies with extended fetal legs, low birthweight, short umbilical cord and primiparity.

Management of the patient with a breech presentation continues to be one of the challenging problems in obstetrics. An important question is whether external cephalic version should be performed or not. After the report by Saling & Müller-Holver (1975) that external version could be performed under β-sympathomimetic tocolysis in the 37th week several clinics have reintroduced external cephalic version and report beneficial results (Fall & Nilsson 1979; Pluta *et al.* 1981; Hofmeyr 1983).

The decision as to whether external version should be carried out, and when it should be performed depends on whether a spontaneous cephalic version is expected or not. Until now there have been, to our knowledge, no systematic studies of spontaneous cephalic version. The aim of the present investigation was to study a population of patients with the fetus in breech presentation during the last trimester to ascertain when spontaneous cephalic version occurred and to assess correlating factors.

Subjects and methods

From July 1982 until October 1983, 4600 patients participated in a general ultrasonic screening examination in the 32nd week of gestation at the Department of Obstetrics and Gynaecology, University Hospital of Lund, Sweden. A total of 310 (6·7%) singleton breech presentations were identified, and the following variables were assessed in each: fetal biparietal diameter, abdominal diameter, femur length, fetal posture, and placental location.

The patients were followed prospectively at the maternal health care centres and the fetal lie was checked weekly by manual palpation. When it was not possible to establish the fetal lie by palpation another ultrasound examination was performed. All patients were delivered at the delivery ward in Lund, and details of the deliveries were obtained from the hospital records.

To investigate factors associated with spontaneous version to cephalic presentation the series has been divided into two groups: those with persistent breech presentation (PB group) and those in whom spontaneous cephalic version occurred (SCV group).

Statistical methods

The χ^2 and Student's t-test were used for group comparisons. P-values $<0{\cdot}05$ were regarded significant.

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Results

At delivery breech presentation had persisted in 133 patients (43%) and spontaneous version had occurred in 177 (57%). Besides the 133 patients with a fetus in breech presentation seven others (5%) were delivered of an infant in breech presentation during the study period. Four of these infants had been in cephalic presentation and three in transverse lie at the screening scan at 32 weeks.

Table 1 lists the ultrasound findings at 32 weeks gestation in the two groups (PB and SCV). Fetal size, measured by biparietal and abdominal diameter and femur length, did not differ between the two groups, nor did the location of the placenta. The fetal posture differed between the two groups. Fetuses with their legs flexed at the knees occurred significantly more often ($P<0{\cdot}001$) in the SCV group (52%) than in the PB group (20%). In 80% of the patients with persistent breech presentation the fetus had extended legs at 32 weeks.

Preterm delivery occurred more often and delivery was significantly earlier ($P<0{\cdot}001$) in the PB group compared with the SCV group (Table 2). Fetal weight and length and umbilical cord length were all significantly smaller in the PB group. The differences between the two groups with respect to fetal size could not be explained by the tendency to earlier delivery in the PB group since the difference remains when the two groups were compared within six gestational age subgroups (Table 3).

Primiparity showed a positive correlation with persistent breech presentation ($P<0\ 001$). The probability of a spontaneous version to cephalic presentation differed significantly between primiparae and multiparae ($P<0{\cdot}001$). In multiparae a history of a previous breech delivery markedly decreased the probability of spontaneous version. The probability of a spontaneous version in relation to increasing fetal maturity for primiparae and multiparae with and without previous breech deliveries is shown in Fig. 1; the probability of a spontaneous version occurring in the 32nd week is 78% for multiparae with no previous breech delivery. For multiparae with previous breech presentation the probability is 32% and for primiparae, 46%. The corresponding values in the 37th week are 28, 7 and 8%, respectively.

Discussion

In the present study a very high proportion of breech deliveries were already identified as breech presentations at 32 weeks (133 out of 140; 95%). Thus spontaneous podalic version occurred only rarely during the last trimester.

Persistent breech presentation showed a positive correlation with a number of factors known to be associated with breech presentation such as a lower fetal weight, shorter umbilical cord, extended fetal legs, and first pregnancy. The ultrasound scans at 32 weeks revealed no differences between the two groups except that flexed knees were seen more frequently in the

Table 1. Ultrasound findings at 32 weeks gestation in the persistent breech group and the spontaneous cephalic version group

Ultrasound findings	Persistent breech ($n = 133$)	Spontaneous cephalic version ($n = 177$)
Fetal size		
Biparietal diameter (mm), mean (SD)	82 2 (4·4)	82 6 (3 9)
Abdominal diameter* (mm), mean (SD)	90·4 (5·6)	91 2 (5 4)
Femur length (mm), mean (SD)	62·3 (2 8)	62 3 (2·9)
Fetal posture		
Legs flexed at the knees	27 (20%)	92 (52%)†
Legs extended	106 (80%)	85 (48%)
Placenta location		
Fundal	49 (37%)	65 (37%)
Anterior	53 (40%)	91 (51%)
Posterior	31 (23%)	21 (12%)

* Mean of anterior-posterior and transverse diameters.

† Significant difference between the two groups, $P<0{\cdot}001$.

Table 2. Clinical data at delivery in the persistent breech group and the spontaneous cephalic version group.

Clinical data	Persistent breech ($n = 133$)	Spontaneous cephalic version ($n = 177$)
Maternal		
Age (years)	29·1 (5·4)	29·7 (5·4)
Primiparae	70 (53%)	42 (24%)*
Multiparae	63 (47%)	135 (76%)
Preterm delivery (<37 weeks)	11	1*
Gestation at delivery (weeks)	38·8 (1·8)	39·7 (1·2)*
Fetal		
Birthweight (g)	3268 (565)	3587 (522)*
Length at birth (cm)	49·9 (2·4)	50·6 (2·1)*
Head circumference (cm)	35·3 (1·5)	35·3 (1·3)
Weight of placenta (g)	583 (147)	607 (124)
Length of umbilical cord (cm)	53·5 (13·4)	60·5 (13·2)*

Unless indicated results are mean (SD).
*Significant difference between the two groups $P<0·001$.

Table 3. Birthweight (g) in relation to gestational age in the persistent breech group and the spontaneous cephalic version group

Gestational age (weeks)	Persistent breech	Spontaneous cephalic version
37	2888 (532)	2983 (652)
38	3103 (239)	3317 (413)
39	3361 (510)	3400 (550)
40	3504 (434)	3773 (495)
41	3651 (382)	3908 (663)
42	3433 (387)	3756 (439)

Results are means (SD).

SVC group, whereas extended fetal legs occurred more often in the PB group. It has been suggested previously that the extension of fetal legs was a significant factor in the aetiology of breech presentation (Tompkins 1946; Stabler 1947), since it has been assumed that the extended legs could prevent the infant from kicking himself round. However, in the present study extended legs were closely associated with primiparity and the influence of these two factors could not be separated from each other. It is reasonable to assume that the increased tone in the abdominal wall in primiparae (see below) could predispose to extended legs and it is difficult to determine if extended legs are a primary or secondary factor in the aetiology of breech presentation.

The proportionally lower weight of infants in breech presentations was first noted by Von Numers (1952) and has been confirmed in many investigations since. It has been suggested that the breech fetus with a proportionally lower weight may be capable of less vigorous movements and so be less likely to turn around (Kauppila 1975), or that a change in the relative volumes of the fetus and amniotic fluid could make the fetus less mobile (Schrage 1973). The present study confirms these associations and indicates that impaired fetal growth during the last trimester seems to favour a persistent breech presentation. Analogous findings have been reported at external version of breech presentation, where the small size of the fetus seems to increase the

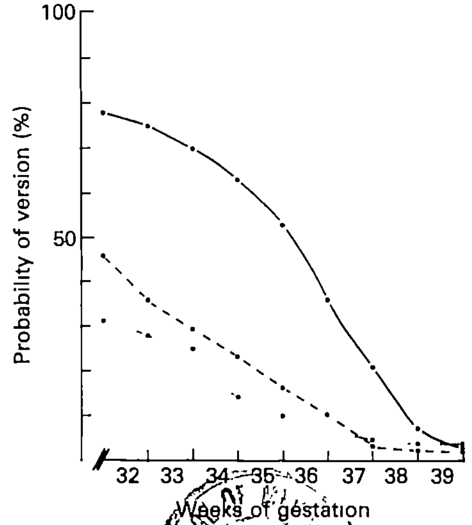

Fig. 1. Probability of spontaneous cephalic version during the last trimester for primiparae (•– –•) and multiparae with (•······•) and without (•——•) previous breech delivery.

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difficulty in fetal manipulation (Kirkinen & Ylöstalo 1982).

That a short umbilical cord could prevent version is widely accepted (Manzke 1978), whereas the significance of the location of the placenta for version of breech presentation is more debatable. Fianu & Václavinková (1979) demonstrated a correlation between cornu–fundal location of the placenta and failed attempts at external version, whereas Kirkinen & Ylöstalo (1982) were unable to demonstrate such an association but claimed that the anterior wall placenta is unfavourable for external cephalic version. The present study reveals no association between spontaneous cephalic version and placental position.

The likelihood of a spontaneous version to vertex presentation in the last trimester is closely correlated with parity and whether or not previous breech deliveries have occurred. The inability of the fetus to turn around in primigravidae is probably due to the tense abdominal wall in these women.

Contrarily, in multiparae with no previous breech delivery, spontaneous version to vertex occurred frequently and nearer the time of delivery. The high incidence of spontaneous cephalic version even at 36–37 weeks (25%) has previously been reported in studies of external version (Fall & Nilsson 1979; Van Dorsten *et al.* 1981).

Breech presentation in a previous pregnancy significantly reduces the chance of spontaneous version to vertex. This is probably due to a special characteristic of the woman's uterus or abdominal cavity. Similar findings have previously been reported by Tompkins (1946), who noted that if the first infant in a family was breech-born, the second was also breech-born in 9·4%, whereas if the first was vertex born, breech delivery only occurred in 2 4%.

As the tendency for breech presentation differs considerably between primiparae and multiparae, it seems logical to take this into account in a discussion about attempting external cephalic version. We suggest that external version in primiparae could, by preference, be performed 1–2 weeks earlier than in multiparae in whom the 37th week seems an appropriate time. The value of external version in multiparae with a previous breech delivery needs further investigation.

Finally, several recent studied have shown that tocolysis significantly facilitates external version (Fall & Nilsson 1979; Van Dorsten *et al.* 1981). Since the high incidence of breech presentation in primiparae may be due to increased uterine tone, it is interesting to speculate if tocolysis could influence the occurrence of spontaneous cephalic version in primiparae with breech presentation. Such a study is in progress.

Acknowledgments

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Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance

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Summary. Since the umbilical arteries carry fetal blood to the placenta we studied flow velocity waveforms in these vessels with a simple continuous wave Doppler system to assess placental blood flow. The ratio of peak systolic to least diastolic (A/B) flow velocity was measured as an index of placental flow resistance. In 15 normal pregnancies there was a small but significant decrease in this ratio through the last trimester. The A/B ratio was measured on 436 occasions in 168 high-risk pregnancies. In 32 of 43 fetuses subsequently shown to be small for gestational age there was an increase in placental flow resistance with reduced, absent or even reversed flow in diastole. This finding was also present in the one fetus which died *in utero*. Serial studies in patients with fetal compromise indicated increasing flow resistance, a reverse of the normal trend. These results were not available to the clinician yet of 24 fetuses born before 32 weeks 13 had a high A/B ratio, and all of them were born electively. Maternal hypertension was associated with an increase in fetal placental flow resistance. The umbilical artery A/B ratio provides a new and non-invasive measure of feto-placental blood flow resistance.

Blood flow to the placenta through the umbilical vessels is essential to provide the fetus with oxygen and nutrients necessary for growth and development. Blood flow has traditionally been considered in terms of pressure/resistance, but may also be measured as the product of vessel area and mean velocity. Blood flow velocity may be measured by Doppler ultrasound (Gill 1979); the moving column of red blood cells acts as a reflector, scattering the ultrasound beam and altering the frequency of the returned signal by an amount proportional to their velocity. In the intact human fetal circulation flow has been measured in the umbilical vein and fetal aorta with these methods (Gill *et al.* 1981; Eik-Nes *et al.* 1980). The major limitation in the application of these methods is the measurement of vessel size. An error of 0.5 mm becomes unacceptable for vessels smaller than 5 mm and pulsatile flow means the diameter is constantly changing.

There is, however, much information in the velocity waveform. With each heart beat a pressure pulse travels down the arterial tree, and is the resultant of forward compression waves created by the ejection pulse of the heart and reflected waves from arteriolar terminations and other near branching points of the arterial tree (Taylor 1965; McDonald 1974). The velocity of blood flow at a point in the circulation is determined by the pressure gradient which exists between that point and closely neighbouring points downstream. If peripheral resistance is high then the incident pressure pulse is highly reflected and returns to cancel the latter part of the pressure pulse. This results in zero or even

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negative pressures, and therefore low or even reversed blood flow in diastole. In contrast, a low-resistance bed allows onwards travel of the pressure pulse wave almost unaltered and thus high diastolic flow velocities. The velocity waveform thus provides important physiological indicators about the pumping heart, vessel wall condition and downstream peripheral resistance (Skidmore & Woodcock 1980). In degenerative arterial disease there has been much more attention paid to these waveforms, but it is in the fetal circulation, more than at any other period of life, that one might expect arterial velocity waveforms to obey haemodynamic principles of laminar flow. Waveforms have been recorded from the umbilical artery in normal pregnancy (McCallum *et al.* 1978; Fitzgerald & Drumm 1977; Stuart *et al.* 1980). In the present study we examined velocity waveforms in the umbilical artery in both normal pregnancy and situations of suspected 'placental insufficiency' subsequently resulting in the birth of a growth-retarded infant, to derive pathophysiological information about placental flow resistance and assess the diagnostic potential of this simple measurement. A preliminary report of this work has been given (Giles *et al.* 1982).

Patients and methods

Recordings were made from the umbilical artery in the cord. A real-time scanner was first used to locate the umbilical cord and the hand-held continuous wave Doppler transducer then directed along the appropriate path with manual adjustments to beam direction to gain maximal signal amplitude and ensure there was only one umbilical artery in the line of sight when recording. The signal was only accepted if it could be displayed simultaneously with the characteristic low frequency signal from the umbilical vein (with an opposite direction of flow). It was also possible by altering slightly the direction of the beam to display both umbilical artery waveforms with flow in opposite directions (beam includes entwined arteries) or one umbilical artery only. The ability to do this was further confirmation that the beam was directed at a segment of the umbilical cord. Because of the marked effect of fetal breathing on the arterial flow (Fouron *et al.* 1975) recordings were not taken during breathing movements, which were obvious in the umbilical vein velocity profile. In a parallel study with a duplex B-mode imaging and pulsed Doppler system this characteristic waveform was confirmed to originate from the umbilical cord. In eight patients the umbilical artery signal was recorded at two sites on opposite sides of the fetus. There was no difference in results.

Blood flow velocity determined frequency shift was recorded using a directional Doppler Blood Velocimeter (Sonicaid BV380) with a 4-MHz continuous wave ultrasound beam to insonnate the fetal vessels. The separated quadrature Doppler signals from this meter were recombined and frequency spectral analysis was performed on this signal (Unigon Angioscan). Frequency offset processing permitted the display of forward and reverse flow on an oscilloscope, as frequency (proportional to velocity) over a time base, with a grey scale intensity modulation. The Doppler signals were simultaneously recorded on audio tape for storage. An oscilloscope recorder (Medelec FOR 1002) was used to provide a tracing of the oscilloscope display onto light-sensitive paper as a permanent record. Direct photography was also used. The spectrum analyser has a high-pass filter to eliminate low frequencies (<300 Hz) attributable to vessel wall movement and so very low flow velocities were not recorded unless the filter was switched out.

In all studies the ratio of the peak systolic velocity (A) to the least diastolic velocity (B) was determined over at least 10 cardiac cycles. The A/B ratio (Fig. 1) is independent of the angle between the ultrasound beam and the direction of flow. Where diastolic flow was absent or reversed the A/B ratio was recorded as >6 (this value was well beyond our normal range). This avoids very high values in the situation where 'B' is low or indeterminate because of filtering. It was possible to switch off the filter but wall motion may be confused with low flow velocities. The A/B ratio has been shown to provide a measure of peripheral

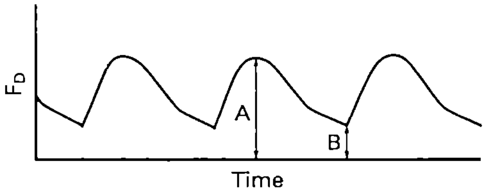

Fig. 1. The A/B ratio is calculated as the ratio of peak systolic (A) to least diastolic (B) flow velocity. The Doppler frequency shift (F_D) is directly proportional to flow velocity.

resistance in the vascular bed downstream from the vessel under study (Gosling 1976).

As a control group, 15 normal pregnancies were studied every 2 weeks from 28 weeks until the onset of spontaneous labour which in all cases occurred after 37 weeks and resulted in the birth of an infant of birthweight greater than the 25th centile. There was ultrasound confirmation of dates in all cases. Studies were carried out in the morning and the women were allowed to have breakfast before the study. All patients were non-smokers.

The study group comprised 168 patients with singleton high-risk pregnancies. In 32 patients the last study was >10 days before delivery and they were excluded from further analysis leaving 136 patients studied on 368 occasions. The mean interval between last study and delivery was 3 days (SD 3·2). This was a consecutive series of patients admitted to the antenatal ward with obstetric risk factors indicating potential fetal compromise (Table 1). A satisfactory recording of the umbilical artery velocity waveform was obtained from every patient. The results of these studies were not available to the clinician managing the patient.

Table 1. Obstetric risk factors in the 136 patients in the study

Suspected intrauterine growth retardation	51
Maternal hypertension	34
Maternal diabetes	18
Renal disease	5
Antepartum haemorrhage	10
Threatened premature labour	6
Poor obstetric history	5
Maternal epilepsy	1
Rhesus isoimmunization	1
Known fetal abnormality	4
Maternal subarachnoid haemorrhage	1
Total	136

Results

In the normal pregnancy group there was a systematic change in the velocity waveform with increasing gestational age. A representative sequential study of umbilical artery flow velocity waveforms is shown (Fig. 2). The A/B ratio in all normal pregnancies decreased over the last trimester of pregnancy (Fig. 3), indicating a decrease in placental flow resistance (relative to the proportion of cardiac output directed to the umbilical arteries).

Of the 136 patients with potential fetal compromise 43 subsequently gave birth to an infant small for gestational age (less than the 10th centile, corrected for parity and fetal sex) and in 22 of them the birthweight was less than the 5th

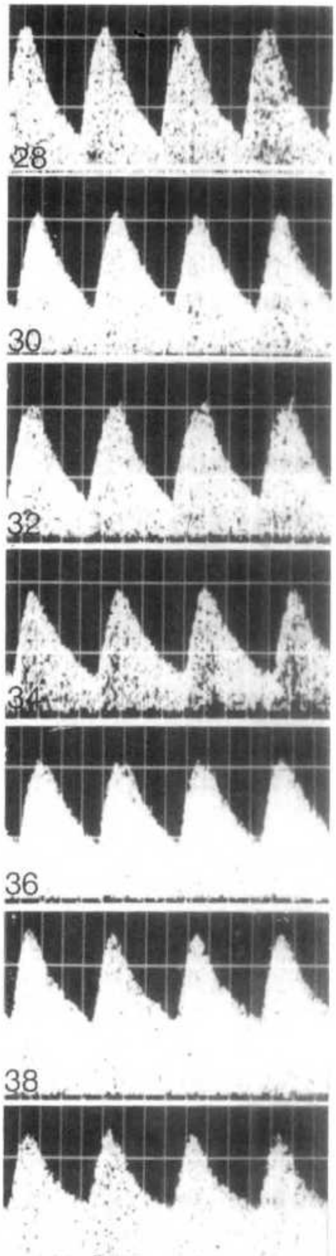

Fig. 2. Serial studies of umbilical artery velocity waveforms in one normal fetus (x axis: 0·1-s time intervals; y axis: 1000-Hz frequency shift interval).

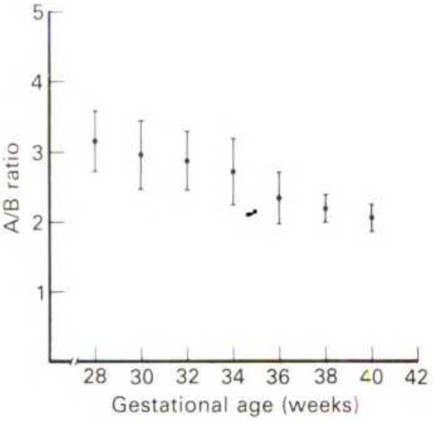

Fig. 3. The mean (±SD) A/B ratio at each 2-week period in 15 normal pregnancies studied serially.

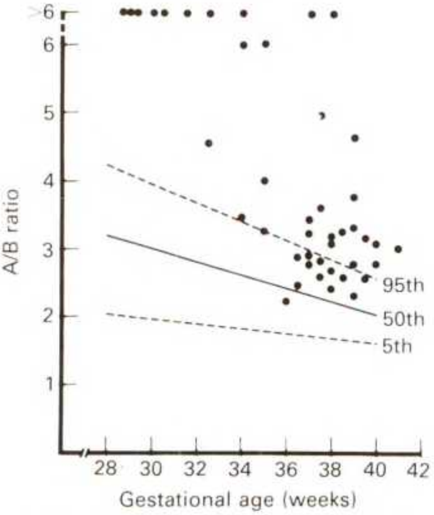

Fig. 4. The last A/B ratio measured in 43 fetuses subsequently born small for gestational age.

centile. The A/B ratio closest to delivery in this group is shown in Fig. 4, against the 5th and 95th centile values derived from the normal group. Only in 12 pregnancies was the A/B ratio in the normal range. Those cases where diastolic flow was absent or reversed are plotted as >6. A representative pregnancy, resulting in the birth of an infant small for gestational age, is shown in Fig. 5. In a 40-year-old patient with renal hypertension, delivered at 34 weeks because of low maternal oestrogens and associated non-reactive cardiotocograph, the A/B ratio increased (Fig. 6) on serial studies indicating increasing placental flow resistance.

The A/B ratio was related to another measure of chronic hypoxia: the 5-min Apgar score. Of 10 infants in the study group with a 5-min Apgar score of ≤6, seven had an A/B ratio beyond the normal range, of the other three infants, one had Werndig Hoffman disease, and two were born at 31 and 35 weeks gestation after premature rupture of membranes and developed severe hyaline membrane disease. One fetus died before delivery at 35 weeks, this pregnancy was associated with a non-reactive cardiotocograph and low oestrogen levels; the A/B ratio was high and there was absence of flow in diastole (Fig. 7).

The last A/B ratios of the 136 study patients are plotted in Fig. 8. There were 24 patients in whom the last study A/B ratio was above the 95th centile value and who did not give birth to small-for-dates infants. Five patients in this group had severe hypertension (diastolic pressure >105 mmHg and proteinuria) and five had insulin-dependent diabetes, all of them were delivered electively because of non-reactive fetal heart rate patterns or low oestrogen levels (less than the 10th centile). Serial studies from one of these patients (Fig. 9) illustrates an increase in the A/B ratio with the deterioration in fetal welfare. The infant was macrosomic and was born electively at 34 weeks. A further 10 of these 24 patients had abnormal fetal heart rate patterns or

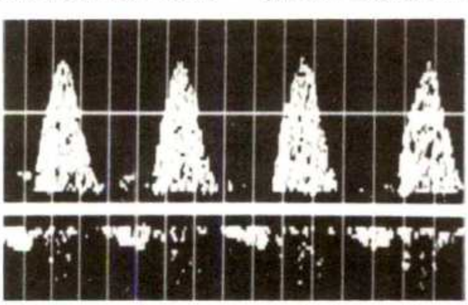

Fig. 5. The umbilical artery velocity waveform at 33·3 weeks in a patient (aged 27 years, para 1+0) who gave birth to a small-for-dates (male, 930 g); illustrating reversal of diastolic flow (x axis: 0·1-s time intervals; y axis: 1000-Hz frequency shift interval).

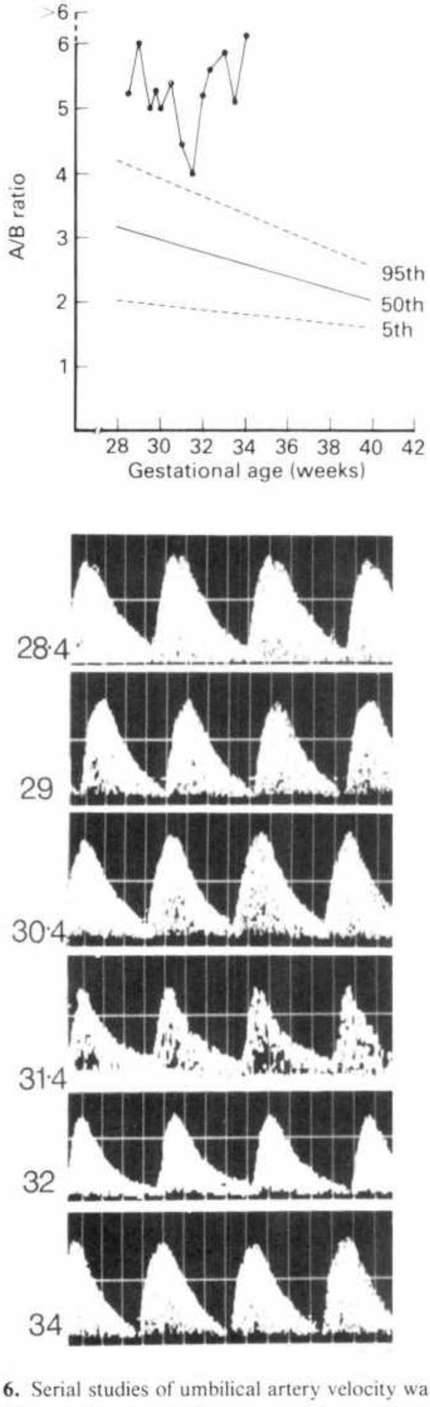

Fig. 6. Serial studies of umbilical artery velocity waveforms in a patient (aged 40 years, para 2+1, with renal hypertension) who gave birth to a small-for-dates infant (male, 1720 g). The A/B ratio is plotted in the upper panel and a selection of the study waveforms are shown in the lower panel with gestational age indicated (x axis: 0·1-s time interval; y axis: 1000-Hz frequency shift interval).

low maternal plasma total oestrogen levels. In the remaining four patients tests of fetal welfare were normal. Of the 80 pregnancies with the last A/B ratio below the 95th centile only 13 had low oestrogen levels or non-reactive fetal heart rate patterns (six of these 13 infants were small for gestational age). In none of them, however, was the tracing considered pre-terminal (non-reactive, late decelerations) (Table 2).

In this study 24 patients were delivered before 32 weeks, and in 13 the final A/B ratio measurement was high with reduced flow velocity or reversal of flow in diastole. All 13 fetuses were delivered electively because of abnormal results of tests of fetal wellbeing or severe maternal hypertension. The other 11 patients delivered before 32 weeks had A/B ratios in the normal range; eight of them had a premature delivery after spontaneous premature labour or membrane rupture (non-elective delivery). The other three were delivered electively for rhesus isoimmunization, fetal abnormality and maternal brain death from subarachnoid haemorrhage, none of the three fetuses was growth retarded and there was no evidence of inadequate placental function. Although the results of umbilical artery waveform analysis were not available to the clinician, the pregnancies with an A/B ratio above the 95th centile were the pregnancies that were delivered electively because of concern about fetal welfare.

A total of 72 patients were studied more than once and none of the patients with a normal outcome had sequential A/B ratios that differed by more than one unit. In the pregnancies with an abnormal outcome, bed rest was associated with a decrease in the A/B ratio in eight patients, although in three this increased again after an initial decrease.

Discussion

This paper reports a new method to monitor placental insufficiency. Recording the umbilical artery velocity waveform provides a direct measure of placental flow resistance. The systolic cardiac impulse propels blood down the arterial tree, and flow is maintained by the pulsatile energy stored and then released from the elastic vessel walls. Flow results from pressure acting against peripheral resistance, vessel wall compliance and blood stream inertia. The extent of downstream impedance determines the degree of reflection of the incident pressure wave. It is the later diastolic part of the waveform that is

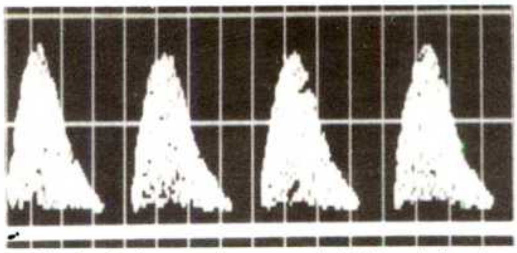

Fig. 7. The umbilical velocity waveform recorded 5 days before intrauterine fetal death in a patient aged 24 years, para 0+0 (x axis: 0·1-s time intervals; y axis: 1000-Hz frequency shift interval).

affected by the reflected wave. High impedance is associated with greater pressure pulse wave reflection and reduced or even reversed (negative) blood flow velocities in diastole (Taylor 1965) (high A/B ratio). If reflection is low, high forward flow velocities continue (low A/B ratio). The A/B ratio provides a measure of impedance or resistance to blood flow downstream from the point of recording. The fetal placental vascular tree is normally a low-resistance bed with resistance decreasing with increasing gestational age, and our findings of decreasing A/B ratios parallel observations of decreasing flow resistance in the fetal lamb in late pregnancy (Dawes 1968). This bed lacks neural control and short-term variations in flow result from change in fetal cardiac output (largely determined by heart rate) and arterial pressure; variations in peripheral resistance will produce longer-term changes in flow.

Study of the umbilical artery velocity waveform in pregnancies with potential fetal compromise revealed most interesting findings. Fetal growth retardation and perinatal hypoxia indicated by a low 5-min Apgar score were clearly associated with an increase in placental resistance (high A/B ratio). Fulminating maternal hypertension was also associated with high resistance in the umbilical circulation. This finding implies a change on the fetal side in association with, or resulting from, the maternal disease and reduction in uterine perfusion. Deteriorating health of the macrosomic diabetic fetus (Fig. 9) also was associated with an increase in placental flow resistance, yet earlier in the pregnancy growth had been excessive.

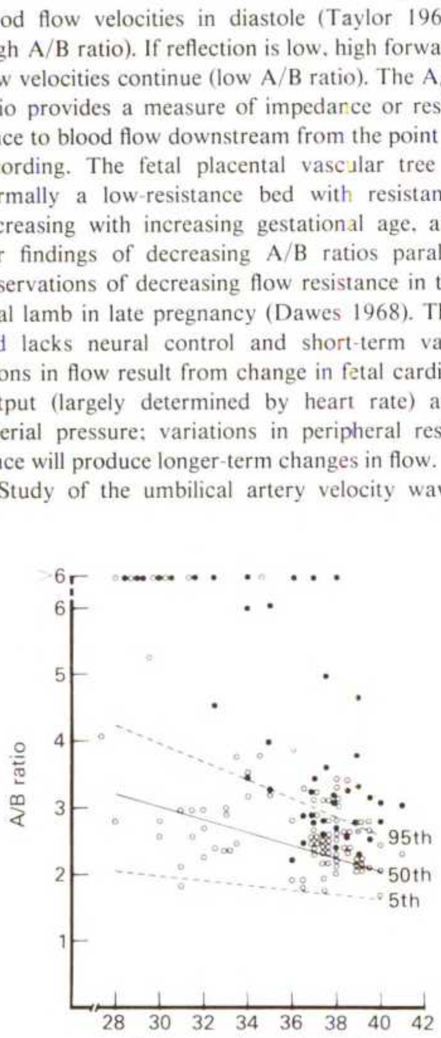

Fig. 8. The last study A/B ratio of all 136 study patients. Those infants born small for gestational age are shown (●).

In the present study the angle of incidence of the ultrasound beam to the umbilical artery was not known. Absolute velocity is therefore not measured but rather the ratio of systolic to diastolic velocity (since the incident angle remains constant). By altering the transducer direction it is possible to estimate the maximum systolic velocity if the incident angle is within the range ±26° of the direction of flow (cosine $0 = 1$ hence observed velocity is maximum if ultrasound beam is in the direction of flow, cosine $26 \simeq 0{\cdot}9$ hence observed velocity is within 10% of maximum if incident angle is $<26°$). In this study we endeavoured to record the maximum systolic velocity, which ensured that a low diastolic velocity or absent velocity was not due to a high incident angle. We have not examined the relations between maximum systolic velocity and pregnancy outcome, but it did appear that an increase in A/B ratio was due to decreasing diastolic flow velocity rather than increasing systolic flow velocity which was not observed.

Placental insufficiency is an obstetric term used to express the functional abnormality which results in failure of fetal growth. Yet the underlying pathology remains uncertain. It may be that maternal blood contains insufficient oxygen or nutrients, or the uterine blood flow may be

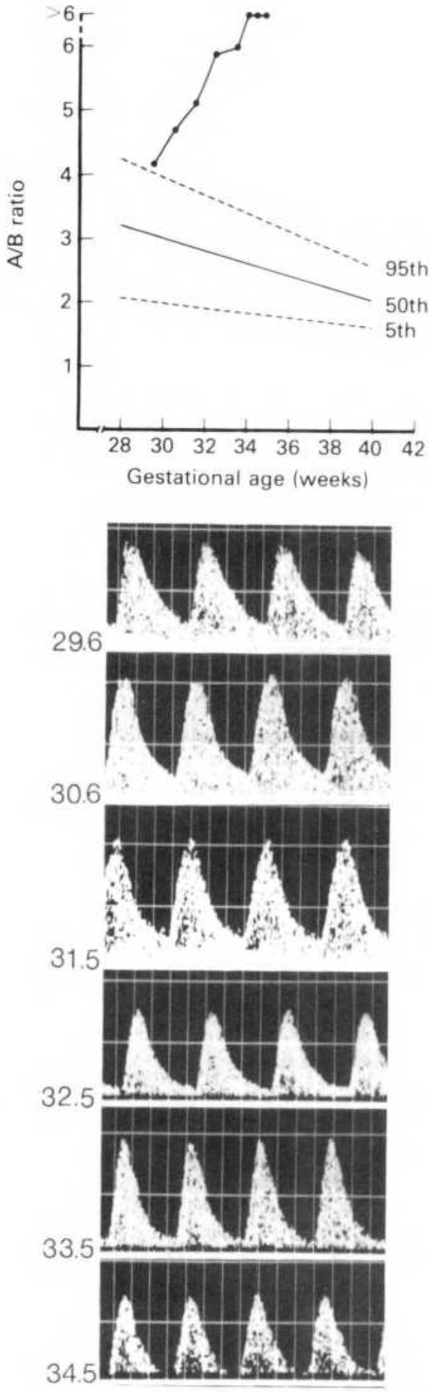

Fig. 9. Serial studies of umbilical artery velocity waveforms in a patient (aged 31 years, para 0+0) with poorly controlled diabetes mellitus who was delivered prematurely (male, 4030 g) because of abnormal fetal heart rate tracing. Upper panel A/B ratio of each study. Lower panel sequential waveforms (x axis: 0·1-s time intervals; y axis: 1000-Hz frequency shift interval).

Table 2. Pregnancy outcomes related to A/B ratio in 136 high-risk pregnancies

A/B ratio	Pregnancy outcome	
	Normal*	Abnormal
Normal	58	22
>95th centile	4	52

* All the pregnancies included in the 'normal outcome' group had normal maternal serum oestriol levels, normal fetal heart rate patterns, birthweights above the 10th centile and Apgar scores ≥7 at 5 min.

inadequate. There may be impairment of exchange across the placenta from maternal to fetal circulation. The fetus may be unable to assimilate an adequate supply of oxygen and nutrients. In this study a group of fetuses who might be described as victims of placental insufficiency were observed to have a high placental blood flow resistance. Further, serial studies show this to increase in contrast to the expected decrease during the last trimester of pregnancy, so that we are reporting a new way to monitor placental adequacy.

In studies of fetal jeopardy it is often difficult to define end points that adequately confirm fetal compromise. In this study birthweight and Apgar score have been used. The occurrence of abnormal placental flow resistance in some of the other patients may indicate that fetal compromise was also present, but deterioration of fetal condition to the defined limits had not yet occurred.

Recording umbilical artery velocity waveforms is simple. The audible Doppler signal is readily heard and distinguished by ear from fetal aorta or maternal vessels. A real time scanner was used to locate a loop of umbilical cord, but with practice the observer was able to find the vessels without this step. It was sometimes difficult to record when the placenta was anterior, but with persistence a 'line of sight' could always be found. A continuous wave ultrasound system is much simpler technically than the pulsed-wave systems duplexed to a B-mode imaging system, and is very portable. The returning waveform is continuously recorded, but with continuous wave Doppler ultrasound, waveforms need to be analysed for variables which are independent of the angle between ultrasound beam and direction of flow in the vessel since this is not measured. The A/B ratio is one such measure.

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Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation

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Summary. Placental microvascular anatomy was correlated with antenatal assessment of the umbilical circulation in 106 patients to further validate the measurement of the A/B ratio (the ratio of peak systolic to least diastolic flow velocity) of the umbilical artery flow velocity time waveforms as an index of blood flow resistance. Three groups of patients were studied: a normal group of 38 uncomplicated pregnancies, a control group of 33 potentially 'at risk' pregnancies with a normal A/B ratio matched by risk factors and gestation with the third group of 35 pregnancies with a high A/B ratio. Placental arterial resistance was quantitated by counting the number of small muscular arteries ($<90\ \mu m$ diameter) in the tertiary stem villi in a standard microscopic field (mean 18·5 fields/placenta). The modal small arterial vessel count was shown to be significantly less in the group with a high fetal risk and a high A/B ratio (1–2 arteries/field) than in both the normal and control groups (7–8 arteries/field). The tertiary villus count did not vary between groups. Antenatal studies of umbilical artery flow velocity waveforms with Doppler ultrasound identify a specific microvascular lesion in the placenta characterized by obliteration of small muscular arteries in the tertiary stem villi.

Blood flow velocity waveforms in the human fetoplacental unit may be studied by continuous wave Doppler ultrasound (McCallum *et al.* 1978; Fitzgerald & Drumm 1977) and volume flow, measured with pulsed Doppler to allow simultaneous imaging to measure cross-sectional area of the vessel under study (Gill *et al.* 1981). In pregnancies associated with fetal growth retardation we have observed a characteristic change in the umbilical artery flow velocity waveform (Trudinger & Cook 1982; Trudinger *et al.* 1985).

Examination of arterial flow velocity waveforms with continuous wave Doppler ultrasound has been used in the study of vascular physiology (Gosling 1976; Jonnart 1981). Various indices have been suggested to assess vascular bed resistance or impedance downstream from the studied artery: the pulsatility index (Gosling 1976; Gibbons *et al.* 1981), the damping factor (Gosling & King 1978), and the ratio of peak systolic to least diastolic velocities or the A/B ratio (Gosling 1976). The decrease in diastolic flow observed in the umbilical artery flow velocity waveforms in association with fetal growth retardation is indicative of increased umbilical placental resistance (Trudinger *et al.* 1985).

The object of this study was to examine the microvascular basis of ultrasound recorded umbilical placental flow resistance. In human pregnancy profound fetal growth retardation has been related to pathological changes in the maternal uterine spiral arteries (Robertson *et al.* 1975; Wallenburg *et al.* 1973*b*; Sheppard & Bonnar 1976). But changes in the umbilical artery velocity waveform are on the fetal side of the placental circulation, and hitherto there has been

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Table 1. Gestation in the three patient groups

Gestation (weeks)	Normal group ($n = 38$)	Control group (normal A/B ratio) ($n = 33$)	Abnormal study group (high A/B ratio) ($n = 35$)
26–29	8	3	8
30–33	10	10	10
34–37	10	10	10
⩾38	10	10	7

no association noted between fetal compromise and consistent morphological changes in the fetal placental structures (Fox 1976). Failure to correlate morphology with disease has been attributed by Fox (1978) to various factors such as too few placentas studied; lack of control groups; consideration of pregnancies of various gestations as a homogenous group; failure to study a maternal complication in isolation; and failure to account for placental changes after death *in utero*.

Since the major arterial pressure change in the placenta (Walsh & Lind 1978) occurs at the level of the small arteries/arterioles in the tertiary stem villi, we counted these vessels in order to quantitate umbilical placental blood flow resistance. This was related to antenatal umbilical artery flow velocity time waveforms.

Patients and methods

Patients

Three groups of patients were studied (Table 1). Group 1 constituted the 'normal' group and included 38 uncomplicated pregnancies without any known fetal or maternal risk factor. Ten of them were delivered at between 38 and 42 weeks gestation, and 28 were delivered preterm after spontaneous labour with no evidence of fetal or maternal compromise. These pregnancies were all accurately dated by early ultrasound and the birthweights were appropriate for their gestational ages (between the 10th and 90th centile) (Tanner & Thomson 1970; Babson *et al.* 1970). The placentas from this group were examined to provide a normal reference range.

Group 2 was the control group consisting of 33 pregnancies referred for fetal assessment with a recognizable risk factor detailed in Table 2. In this group of patients values of umbilical flow resistance, estimated by the A/B ratio, were all within the interquartile range as determined from our studies of normal pregnancies (Trudinger *et al.* 1985).

Group 3, the abnormal study group, consisted of 35 pregnancies, also selected for study because of fetal or maternal risk factors (Table 2), which were noted to have raised umbilical placental flow resistance on Doppler ultrasound study of the umbilical artery. All the patients included in this group had an A/B ratio greater than 3 SD above the mean. Patients with multiple pregnancy or maternal diabetes were not included in this study.

Table 2. Maternal and fetal risk factors in the control and abnormal study groups

Risk factor	Control group (normal A/B ratio) ($n = 33$)	Abnormal study group (high A/B ratio) ($n = 35$)
Clinically suspected fetal growth retardation	17	14
Hypertensive disease in pregnancy	11	19
Renal disease	2	2
Antepartum haemorrhage	3	0

The patients in group 3 were selected for their high A/B ratio and the patients in group 2 were their closest match for gestational age (±2 weeks) and risk factor. Two patients from group 3 could not be matched. The classification of groups was made at the time of study of the umbilical artery velocity waveform and therefore before delivery. In all patients the interval between the last measurement and delivery was <10 days.

Methods

The placentas were collected immediately after delivery, they were weighed and measured and then put in a solution of 10% formalin in normal

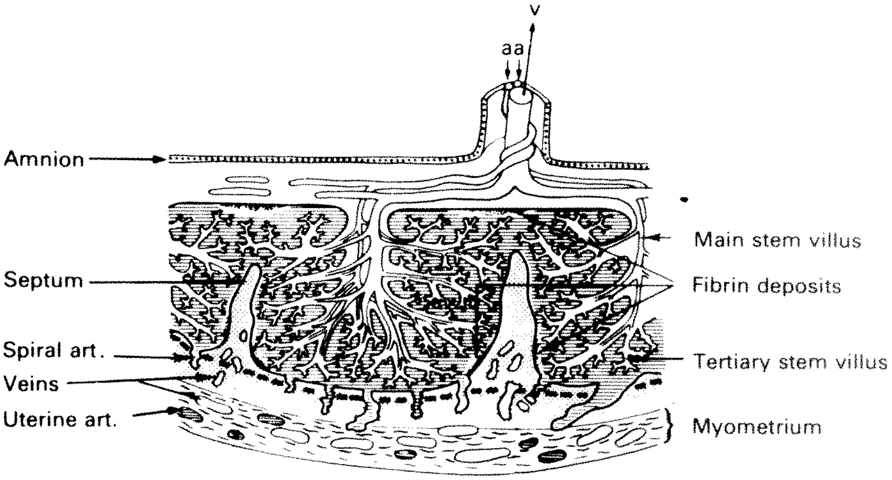

Fig. 1. Cross-sectional view of the human placenta with attached uterine wall. Modified from Walsh & Lind (1978), courtesy Plenum Medical Book Company.

saline. The umbilical cord was clamped early after delivery. The placentas were allowed to fix for at least 5 days before sectioning, then they were cut longitudinally at 1·5-cm intervals and blocks were taken randomly from each placental strip for preparation. All blocks examined were within a zone >2 cm from the cord insertion and >2 cm from the placental margin. Areas of infarction were avoided. Two blocks were counted in each of six placentas, three blocks in 30 placentas, four blocks in 53, five blocks in 14, six blocks in two and seven blocks in one placenta. More blocks were taken from the larger placentas. The sections were stained with a Gomori trichrome one-step stain so that the vascular musculature and the collagen tissue of the placental vessels could be demonstrated.

Small muscular arteries were counted (per ×100 field) in five fields from each block. A slide from each placental block was scanned under low power (×40). The region of the mid-zone of each slide was examined (Thilveris & Baskett 1978) to avoid the subchorionic and basal regions with their fibrin deposits. The following areas were avoided: areas of placental infarction; areas of intervillus fibrin deposition; arterial vessels forming the primary stem and anchoring villi; and histological artifact. Five fields in the midzone were observed on each block moving from left to right (a mean of 18·5 fields was counted per placenta).

The vessel diameter was measured with a micrometer graticule (Graticules Limited) calibrated with a stage micrometer for the respective microscope objective (i.e. ×4, ×10, ×20 and ×40 objectives). We studied the small muscular arterial vessels, and vessel width was measured as the greatest external transverse diameter in a section at right angles to the line of the vessel. In the placenta we defined the following vessels (Boyd & Hamilton 1967): arterioles which are the small vascular structures with either the same diameter or slightly larger than their corresponding capillaries, namely approximately 20 µm in diameter, but distinguished by their muscular coat of at least 1–2 muscle cells in thickness; small arteries of the tertiary stem villi with external diameters of up to 90 µm; and venous channels that attain a muscular coat of only one muscle cell in thickness when their diameter is >50 µm (the venous muscular wall is 2–3 muscle cells in thickness at approximately 200 µm). The venous structures have a noticeably smoother endothelial surface than the arterial structures. From all the field counts for each placenta the modal small arterial count was determined.

Tertiary stem villi were also counted (Fig. 1) in each field to ensure comparability between sections, patients and groups.

The validity of this method of analysis was confirmed by examining for the uniform distribution of vessels and the reproducibility of counting.

Vessel distribution. Twelve placentas, four from each of the three groups, were divided through their longest axes then sectioned into 1·5-cm blocks and every other block was studied. Small arterial vessels and tertiary stem villi were counted on each of these blocks. The sections within 2 cm of the placental edge were excluded due to the high prevalence of intervillus fibrin deposition. Previous investigators have shown that placental structures are not consistent at the periphery (Fox 1976; Boyd *et al.* 1980). We used the same method of statistical analysis (Boyd *et al.* 1980). Only three of the 12 placentas showed any significant difference amongst the six blocks taken and in each of these it was in only one block that the difference was observed. On each occasion this was the block beneath the umbilical cord insertion. Hence, we excluded the 2-cm zone beneath the cord insertion from our study.

Vessel counting. Six placentas were selected at random ('normal' group (2), the control group (1) and the abnormal study group (3)); and three blocks from each were counted (five fields per slide). These slides were randomly numbered and counted blind. The slides were 'recounted' a total of four times over a period of 2 weeks. There was no significant difference between the modal small arterial vessel and tertiary stem villous counts for each placenta (paired t-test). In a further 38 placentas, counts were repeated a second time at least 6 weeks after the original count and without reference to the original result. Again there was no significant difference (paired t-test).

Results

The small arterial counts in the normal and control groups were similar, but there was a strikingly significant difference between these groups and the abnormal study group (group 3) with abnormal umbilical artery velocity waveforms (Wilcoxon, $P < 0{\cdot}01$) (Fig. 2). This striking difference was observed in all gestational subgroups except for the control 26–29 weeks group where the numbers were small ($n = 3$) (Fig. 3). A representative field from a normal placenta (Fig. 4) can be compared with a placenta where there was raised umbilical placental blood flow resistance (high A/B ratio) (Fig. 5) and where the absence of arterial vessels in the tertiary stem villi is apparent. In a number of these abnormal placentas we observed collections of nuclear material that may have represented obliteration of a small artery.

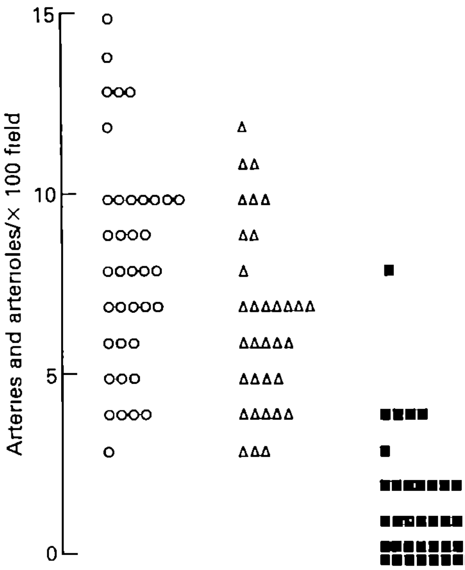

Fig. 2. Modal small arterial vessel counts per ×100 microscope field. Normal group (○), control group (high fetal risk, normal A/B ratio) (△), abnormal study group (high fetal risk, high A/B ratio) (■). The counts in the abnormal group (■) were significantly ($P<0{\cdot}01$) lower than those in the corresponding normal and control groups

There was a weak correlation between small artery count and gestational age in the normal ($r = 0{\cdot}30$, $P<0{\cdot}02$) and control group ($r = 0{\cdot}45$, $P<0{\cdot}02$).

There were no significant differences in the tertiary stem villi counts between the three groups at any gestational age (Fig. 6). Thus the reduction in small arterial counts in the abnormal study group is due to a real loss of these vessels from the tertiary stem villi.

The mean placental weight in the abnormal study group (285 g) was significantly lower than those in the normal (419 g) and control groups (386 g) ($P<0{\cdot}001$). There was the expected overall positive correlation of placental weight with gestational age for all groups. It was thus the larger placenta of the control group which had the high small arterial vessel counts per microscope field magnifying the difference in flow resistance between this and the abnormal study group. There was no statistical difference in the placental weights before and after fixation in 10% formalin (paired t-test).

The prevalence of small-for-gestational age infants and infants with low 5-min Apgar scores

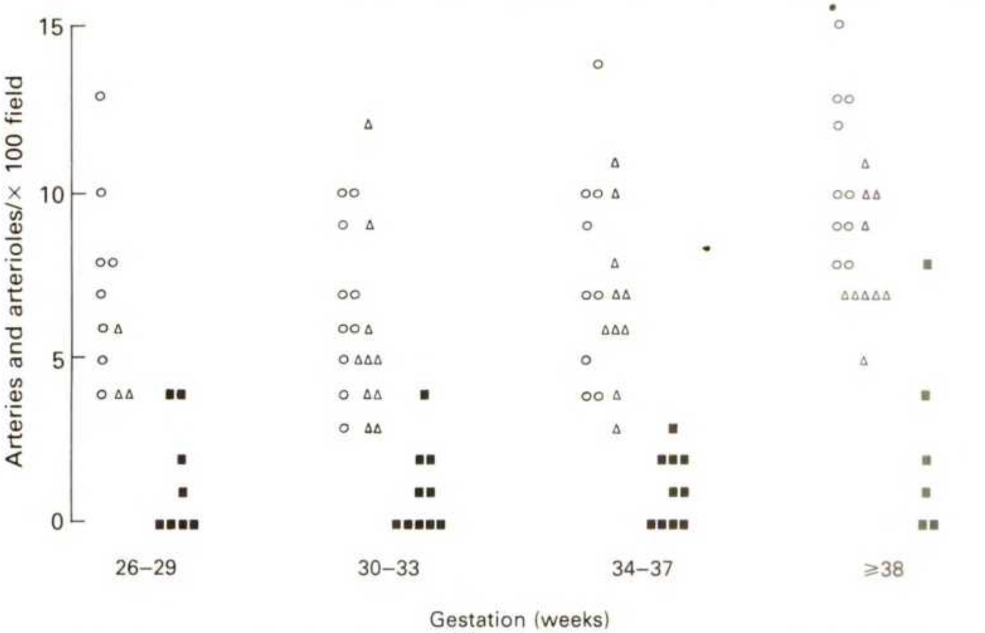

Fig. 3. Modal small arterial vessel counts for each gestational age subgroups. Normal group (○), control group (high fetal risk, normal A/B ratio) (△), abnormal study group (high fetal risk, high A/B ratio) (■). In each gestational age subgroup the counts in the abnormal group (■) were significantly lower ($P<0{\cdot}01$) than those in the corresponding normal and control groups.

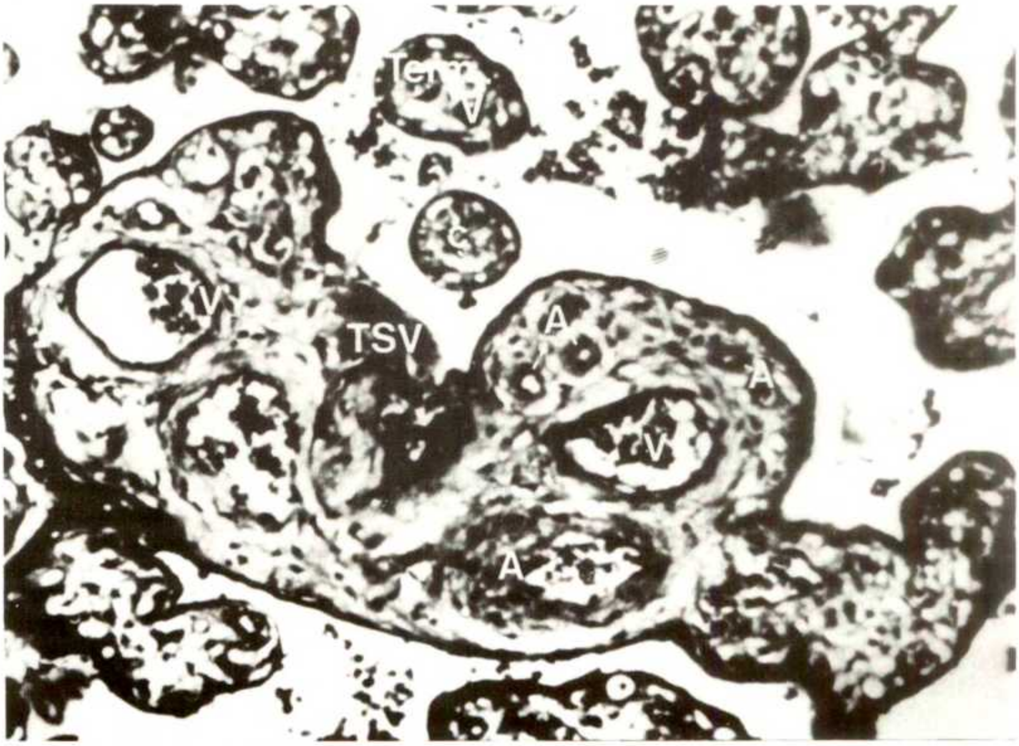

Fig. 4. Placental micrograph from a placenta with normal umbilical placental blood flow resistance (normal A/B ratio) (×240) showing a tertiary stem villus (TSV) and terminal villus (Term. V). Small arterial vessels (A), venous channels (V) and a capillary (c) are indicated.

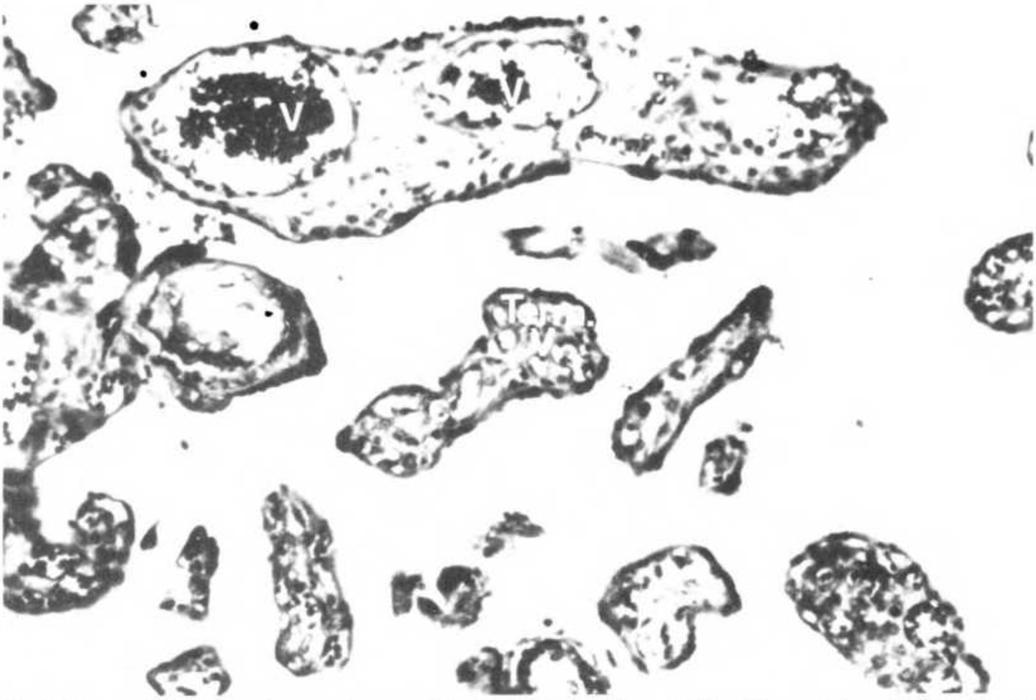

Fig. 5. Placental micrograph from a placenta with raised umbilical placental blood flow resistance (high A/B ratio) (×240) showing a tertiary stem villus (TSV) and a terminal villus (Term. V). Venous channels (V), a capillary (c), and the speculated obliterated small arterial vessel (Obl. A) are indicated.

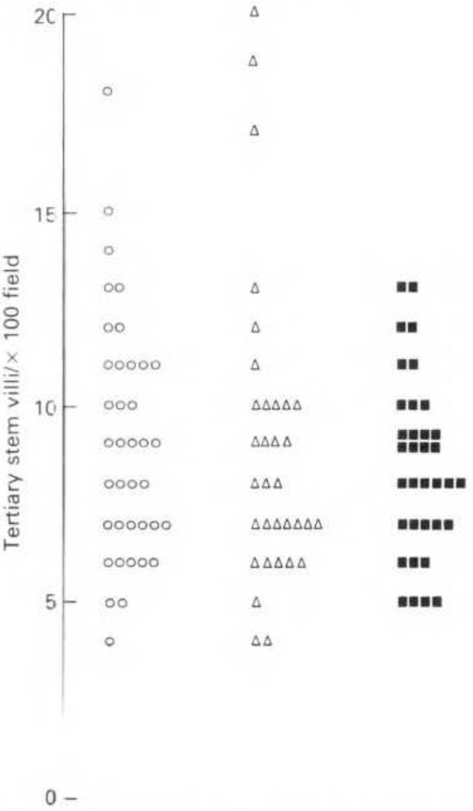

Fig. 6. Modal tertiary stem villi count per ×100 microscopic field. Normal group (○), control group (high fetal risk, normal A/B ratio) (△), abnormal study group (high fetal risk, high A/B ratio) (■).

(<7) illustrates the clinical significance of the abnormal flow velocity waveform. There was a higher prevalence of small-for-gestational-age infants (23 compared with three, $P<0.001$) and infants with Apgar scores of <7 at 5 min (10 compared with one, $P<0.001$) in the abnormal study group than in the control group.

Discussion

This study was designed to relate antenatal umbilical artery flow velocity waveforms with placental microvascular anatomy and followed on from our earlier findings of a correlation between the clinical assessment of fetal growth retardation and the ultrasound measurement of umbilical arterial flow resistance (Trudinger *et al.* 1985). The A/B ratio, a measure of peripheral resistance to blood flow of the umbilical placental circulation, was derived from the velocity waveform. Anatomically peripheral resistance was measured by counting the small arterial vessels in the tertiary stem villi of these placentas. We demonstrated that our antenatal measure of peripheral resistance correlated with this specific microvascular pathology.

In normal ovine pregnancies increasing gestational age is associated with a decrease in resistance to flow in the umbilical placental circulation (Dawes 1968). In human pregnancy a decrease in the A/B ratio (Trudinger *et al.* 1985) is thought to indicate the same change. Our results show there is a small increase in arterial vessel count per microscope field but it is the progressive increase in placental size (weight) and so total number of tertiary stem villi and small arterial channels that principally account for reduced flow resistance. The proportion of fetal cardiac output directed to the placenta through the umbilical arteries is determined by resistance of this bed in relation to the other vascular beds. Loss of small muscular arteries from the tertiary stem villi will cause an increase in resistance.

Our results demonstrate a real arterial 'drop out'. The number of tertiary stem villi did not vary amongst the three groups. The reduced small arterial vessel count implies either a failure of development of a sufficient vascular bed or more likely, since our measurement of placental resistance increased in serial studies of growth-retarded fetuses (Trudinger *et al.* 1985) an obliterative process. Various reasons for the obliterative process can be suggested. The most likely and classically held hypothesis is that of uteroplacental ischaemia. The importance of uteroplacental flow in the nutrition of both the maternal and fetal placenta has been shown by observations of placentas from prolonged pregnancies and fetal intrauterine death (Fox 1978) and from animal models (Wallenburg 1973*a*). Others have postulated that the paravascular capillary network (Boe 1951) which is richest in the sub-chorionic zone is instrumental in placental nutrition (Arts 1961). Another possible cause may be a host versus graft type of rejection of the fetal placental tissue and thus fetal placental vasculature due to a defect in the normal pregnancy blocking antibodies that specifically inhibit maternal responsiveness to paternal antigens. However, to date any immunological evidence of this occurring has been controversial (Fox 1978).

Clinical outcome correlated with the antenatal Doppler study. There was a higher incidence of compromised infants when low Apgar scores at 5 min and small-for-gestational-age were used as indices of morbidity in the group with a high A/B ratio. The control group had similar risk factors to the study group but normal umbilical placental flow resistance.

In our abnormal study group we examined a group of patients who might be described as suffering from placental insufficiency. Histological charactersitics used by investigators in the past include the syncytial knot count, placental infarction, cytotrophoblast hypertrophy, deficiency of vasculoendothelial membranes, fibrinoid necrosis of villi, basement membrane thickening, stromal fibrosis and oedema, apparent placental hypovascularity, and villous maturation (Fox 1978); Fox reached the conclusion that 'a pathological basis for placental insufficiency cannot be defined'. We would disagree with this. The consequences of fetal nutritional deprivation traditionally attributed to placental insufficiency result in chronic perinatal hypoxia (i.e. intrauterine growth retardation, death *in utero*, fetal distress). These are in fact associated with the specific microvascular placental abnormalities demonstrated here and are shown to be definable antenatally with our Doppler ultrasound method. We would suggest the failure to recognize this specific lesion in the past is a consequence of patients being classified by maternal disease or fetal effect rather than the arterial functional disturbance. This is not to imply that the umbilical placental lesion is necessarily primary, it may be determined by factors of fetal or uterine origin, but the placental lesion can be recognized antenatally with new ultrasound technology.

Acknowledgments

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Uteroplacental blood flow velocity-time waveforms in normal and complicated pregnancy

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Summary. A simple continuous wave Doppler ultrasound system for recording arterial flow velocity waveforms in branches of the uterine artery in the placental bed is described. Twelve normal pregnancies were studied serially from 20 weeks to delivery. The diastolic flow velocity expressed as a percentage of the systolic provides an index of downstream vascular bed resistance and perfusion. This always exceeded 50% in normal pregnancy and there was a small increase with gestational age indicative of a decreasing flow resistance. Of the 91 complicated pregnancies, studied because of potential uteroplacental insufficiency and fetal risk, 25 resulted in the birth of an infant small-for-gestational-age. In 15 the uterine artery flow velocity waveform revealed a pattern of low diastolic flow velocity. It is postulated that these represent a subgroup of growth-retarded fetuses in whom there is reduced uterine artery perfusion. Reduced uterine artery diastolic flow velocity in these patients was associated with reduced umbilical artery diastolic flow velocity on the fetal side of the placenta. In contrast the 10 small-for-gestation infants associated with normal uterine artery waveforms suggest a primary fetal cause. Twelve patients with severe hypertensive disease of pregnancy were studied. Nine were associated with reduced uterine artery diastolic flow velocity (reduced uterine artery perfusion) consistent with vasospasm in the branches of the uterine artery in the placental bed.

Measurement of uteroplacental blood flow in pregnancy has long been of interest to the obstetrician but even in the experimental animal this has been difficult (Dawes *et al.* 1968*a*). The uncertain contributions of the uterine arteries of either side and the ovarian arteries makes single vessel measurements difficult to interpret. In addition, the uterine blood flow is partitioned between the placenta and the myometrium. In the maternal ewe a value of 200–250 ml/min/kg uterus has been measured (Huckabee *et al.* 1972). The use of labelled microspheres best allows measurement of flow to the uteroplacental bed but repeated observations produce changes as small vessels are occluded (Clapp *et al.* 1982). The cause of the uterine hyperaemia in response to placental implantation is unknown (Rankin & McLaughlin 1979). Alterations in uteroplacental flow in association with pregnancy complications, particularly hypertension and growth retardation, have been indirectly measured (Browne & Veall 1953; Kääř *et al.* 1980).

Doppler ultrasound provides a method of measurement of blood flow velocity—the moving column of red blood cells scatters and reflects an insonnating beam with a frequency shift (the Doppler frequency shift) proportional to its velocity. Flow is the product of mean velocity

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across the vessel and its cross-sectional area (Gill 1979). The flow velocity-time waveform provides much information and does not require knowledge of vessel dimensions. It is the result of the cardiac impulse travelling down the arterial tree to the small arteries and arterioles where peripheral resistance regulates onwards capillary perfusion (Macdonald 1974; Taylor 1975; O'Rourke 1982). If peripheral resistance is high then the pressure pulse wave travelling down the arterial tree is highly reflected and there is little flow on into the capillary bed. Hence diastolic flow velocity is low and the ratio of peak systolic to diastolic flow velocity is high. This ratio has been used as a measure of downstream resistance (Gosling 1976). Flow is determined by pressure acting on resistance ($Q = P/R$). Changes in flow will follow changes in resistance.

A method of recording flow velocity-time waveforms of the uterine artery using pulsed Doppler ultrasound has been reported (Campbell *et al.* 1983). In this study we describe a simple method for studying the waveforms of a branch of the uterine artery in the placental bed using continuous wave Doppler ultrasound and the changes in the waveform in normal and complicated pregnancies.

Patients and methods

The uterine artery flow velocity waveforms were recorded from branches in the placental bed. A real-time ultrasound scan was first carried out to identify the site of placental implantation. A continuous wave directional Doppler ultrasound (Sonicaid Vasoflo) transducer (4 MHz) was then directed at the placental bed and 'searched' until the characteristic sound of the uterine artery was heard. Where possible the centre of the placental bed was examined. When the placenta was implanted posteriorly a more peripheral part of the bed was recorded mid-way along the lateral uterine margin. The line of interrogation of the continuous wave transducer was rechecked by real-time scan after vessel recording. Spectral analysis of the Doppler signal was carried out in real-time (Unigon Angioscan) and the waveform displayed on an oscilloscope. Hard-copy records were provided by an oscilloscope recorder onto light-sensitive paper. The audio Doppler signal was also recorded.

To confirm the origin of the recorded waveform the transducer of a mechanical sector scanner with a pulsed Doppler facility (Honeywell Ultra Imager) was directed along exactly the same line as the continuous wave Doppler transducer. On the B-mode image obtained the Doppler sample volume was adjusted up and down the line of sight until the same flow velocity waveform recorded with our continuous wave system was heard and seen. Ten normal and five complicated pregnancies were studied in this manner. In all cases a waveform identical to that obtained with our simple continuous wave Doppler system was identified when the sample volume was located in the uteroplacental bed beneath the placenta (Fig. 1). We are unable to determine whether recordings are taken from radial or arcuate arteries in the placental bed. They are analysed for a parameter representing resistance downstream from the point of recording.

At least five waveforms were obtained for analysis. The systolic peak, dicrotic notch and diastolic plateau velocities were recognized. The end-diastolic velocity was very similar to the end-systolic velocity at the base of the dicrotic notch and was used in measurement as it was most readily reproduced. The end-diastolic velocity was expressed as a percentage of the systolic peak

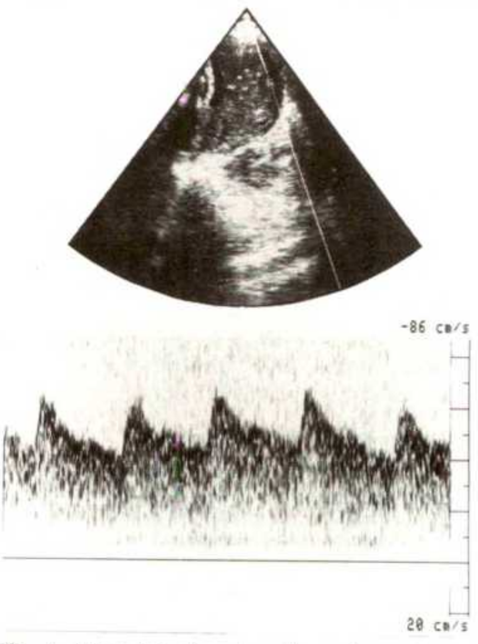

Fig. 1. Recording the uteroplacental arterial flow velocity waveform. The sample volume is indicated by the short lines on either side of the line of sight and is located in the bed of the placenta. The waveform recorded is the lower frame.

velocity. This is the inverse of the A/B ratio and is used as an index of peripheral resistance.

Reproducibility of waveforms was also tested in five normal and five complicated pregnancies. The same patient was examined sequentially by two observers without knowledge of the other's results. There was no difference (paired *t*-test) in diastolic flow as a percentage of systolic flow velocity.

In addition, in all studies, the fetal umbilical artery flow velocity waveform was recorded using the method previously described by us (Trudinger & Cook 1982; Giles *et al.* 1982; Trudinger *et al.* 1985). In this way fetal umbilical–placental arterial waveforms could be compared to maternal uteroplacental arterial waveforms.

Uterine artery flow velocity-time waveforms were recorded through 12 normal pregnancies from 20 weeks to spontaneous delivery on a total of 83 occasions. All patients had ultrasound confirmed dates and delivered an infant of birthweight appropriate for gestational age (above the 25th centile). Seven patients were primiparous and five multiparous but parity was shown not to influence the waveforms. All patients were non-smokers and studies were generally carried out in the morning after an unrestricted breakfast. Patients were resting for at least 30 min before the study and examined in the semi-recumbent position.

Uteroplacental waveforms were recorded in 91 complicated pregnancies where there was considered to be an increased fetal risk due to uteroplacental insufficiency. All patients were at rest in hospital at the time of study. The principal reason for study was suspected fetal growth retardation (small uterus, other abnormal fetal welfare tests) (44 patients) or hypertension (19 patients). Other reasons for study were renal disease (3), maternal diabetes (14), antepartum haemorrhage (3), poor obstetric history (3) and miscellaneous (5). In all these patients the interval between the last study and delivery was <7 days. Sixty-two patients were studied more than once (total studies 164) but the last study was used for our analysis. There were no patients in whom a waveform could not be recorded.

Results

Normal pregnancy

The uteroplacental artery flow velocity-time waveforms show a high diastolic flow velocity relative to the systolic peak (indicating low resistance, high flow). In isolated observations in the first half of pregnancy we have observed much lower diastolic flow velocities in normal pregnancy and so there does appear to be a change with the high flow low resistance pattern at the site of placental implantation established by 20 weeks. Throughout the last 20 weeks of pregnancy there was a small increase in the diastolic flow velocity relative to peak systolic flow velocity (Fig. 2), illustrated in Fig. 3 by serial studies from one patient. On the basis of these results 90% confidence intervals for the diastolic flow velocity as a percentage of the systolic peak velocity were calculated for normal pregnancy.

Complicated pregnancy

Of the 91 patients in this group, who were studied because of potential fetal risk, 25 gave birth subsequently to infants small-for-gestation (less than the 10th centile) and in 15 of them the uterine artery waveform showed diminished diastolic flow velocity (less than our 5th centile) indicative of high resistance low flow (Fig. 4). Of the 25 small-for-gestation infants, 13 had a birthweight less than the 5th centile and a similar proportion, eight, had abnormal uterine waveforms.

Of the 12 patients with severe hypertension (diastolic blood pressure >105 mmHg plus proteinuria >1 g/24 h), nine had abnormal uterine waveforms with a low flow velocity in diastolie (Fig. 4).

Of the 91 patients in the total study group 28 had low diastolic flow velocities (Fig. 4) and 20 of them had severe hypertension or fetal growth retardation. Two of the other eight had very low diastolic flow velocity (<40%): one of them showed an abnormal fetal heart rate pattern at 32 weeks which prompted delivery (? acute reduction in uterine perfusion) and the other (studied at 39 weeks) had familial hyperlipidaemia and diabetes (? vascular lesion). The remaining six patients had values close to the lower limit of the normal range.

Three infants died in the early neonatal period. In all three pregnancies the uterine artery waveform pattern showed an extremely low diastolic flow velocity (<20%). One patient had severe hypertension at 28 weeks and two infants were profoundly growth-retarded.

Of the 91 complicated pregnancies 22 had a low umbilical artery diastolic flow velocity ratio on the fetal side of the placenta, less than the 5th

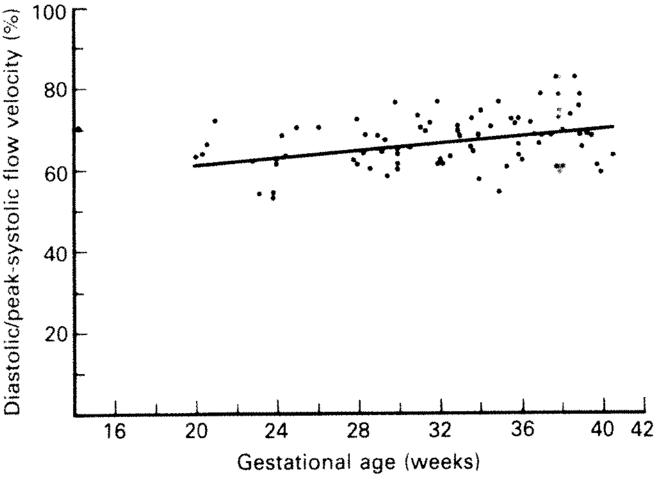

Fig. 2. Diastolic flow velocity/peak-systolic flow velocity (%) in 12 normal patients studied on 83 occasions from 20 weeks gestation. $y = 0{\cdot}426x + 52{\cdot}694$; $r = 0{\cdot}344$; $P<0{\cdot}01$.

centile value reported previously (Giles *et al.* 1982; Trudinger *et al.* 1985). Eleven of these 22 had an abnormal uterine artery waveform with a low diastolic flow velocity, a significantly higher prevalence than that found in the patients with a normal uterine waveform (11 out of 63) (χ^2, Yates correction, 3·928, $P>0{\cdot}05$) (Table 1). Of the 11 patients with a very low uterine artery diastolic flow velocity (<40%) (see Fig. 4) it was the seven who were delivered of a small-for-gestation infant who exhibited a low umbilical artery diastolic flow velocity. The other four did not show this abnormal fetal umbilical artery waveform. Very low uterine artery diastolic flow (high resistance) is therefore associated with low umbilical artery diastolic flow and growth retardation. Of the 25 patients with small-for-gestation infants there were only five in whom both circulations showed a normal pattern. Only two of the 12 patients with severe hypertension showed an abnormal fetal umbilical artery waveform, one of whom is illustrated (Fig. 5).

The relation between centile birthweight and uterine artery velocity waveform is shown in Fig. 6 for all pregnancies studies. Low birthweight was most commonly represented in the group of patients with values outside the normal range. However, in the group of patients with values within the normal range, 10 infants had a birthweight less than the 10th centile, 12 between the 10th and 25th centiles, 27 between the 25th and 75th centiles and 12 greater than the 75th centile.

Table 1. Relation between intrauterine fetal growth and maternal uterine and fetal umbilical artery waveforms

	Birthweight for gestation	
Artery waveform	Appropriate	Small
Uterine normal (normal diastolic flow velocity)	53	10
Umbilical		
Normal	47	5
Abnormal	6	5
Uterine abnormal (low diastolic flow velocity	13	15
Umbilical		
Normal	11	6
Abnormal	2	9

Discussion

We have demonstrated that flow velocity-time waveforms from branches of the uterine artery in

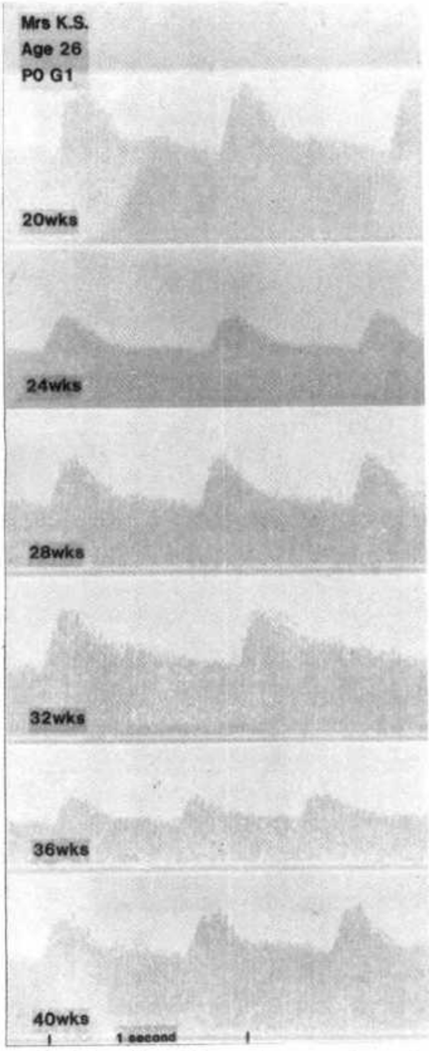

Fig. 3. Serial studies of the uterine artery flow velocity-time waveform in one normal patient.

the placental bed can be recorded. The continuous wave Doppler system we have used is very simple and less expensive than a pulsed Doppler system (Campbell *et al.* 1983). The long sample volume makes vessel location quick and study time short. The placental bed was first located with a real-time B-mode scan. After 20 weeks gestation in normal pregnancy there is a high diastolic flow velocity consistent with a high flow, low resistance vascular bed. This has been quantitated by expressing the diastolic flow velocity as a percentage of peak-systolic flow velocity. The use of this ratio avoids measurement of the angle between ultrasound beam and direction of flow necessary to calculate volume flow since it is equal in systole and diastole. The uterine artery waveforms in severe hypertension and some cases of profound growth retardation show a low diastolic flow velocity, indicating high resistance downstream from the point of recording.

Blood flow is related inversely to resistance ($Q = P/R$) and this is the principal determinant of flow when pressure does not vary widely. In ovine pregnancy, direct measurements (Clapp *et al.* 1982) reveal a progressive increase in uterine blood flow which is associated with a progressive decrease in resistance attributed to a progressive increase in cross-sectional area of the uterine vascular bed. The pressure gradient in fact decreases with gestational age. Our data for normal human pregnancy support the occurrence of this same process, over the whole of the last half of pregnancy. Volume blood flow may also be altered by changes in heart rate. The duration of the diastolic plateau velocity makes this unlikely to affect our measure of resistance.

Abnormal maternal uterine artery waveforms were associated with 60% of the growth-retarded fetuses. This proportion was the same for the infants with birthweights less than the 10th and less than the 5th centiles. This suggests that only in some cases of growth retardation is a change in uterine perfusion a primary event whilst in the others the fetus is small despite normal uterine

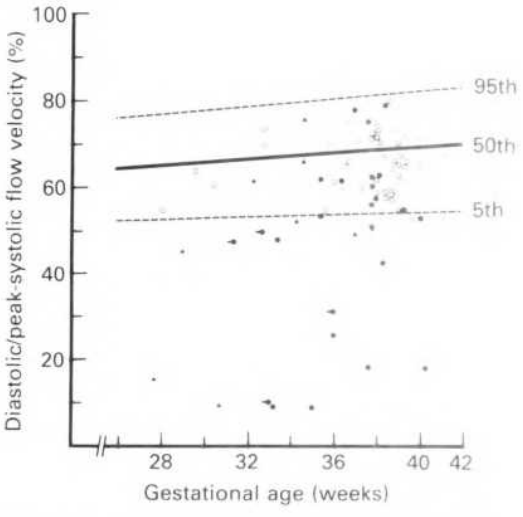

Fig. 4. Antenatal uterine artey flow velocity in 91 complicated pregnancies (normal centile range indicated): ○ birthweight appropriate-for-gestation; ● birthweight small-for-gestation (SGA); ▲ severe hypertension; ▬● hypertension + SGA.

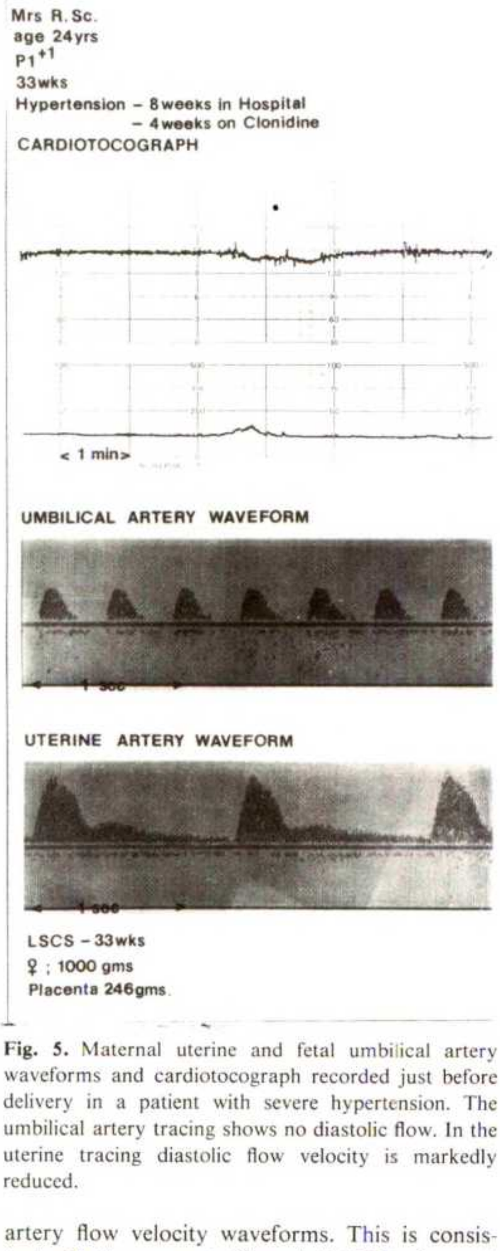

Fig. 5. Maternal uterine and fetal umbilical artery waveforms and cardiotocograph recorded just before delivery in a patient with severe hypertension. The umbilical artery tracing shows no diastolic flow. In the uterine tracing diastolic flow velocity is markedly reduced.

artery flow velocity waveforms. This is consistent with the concepts (Campbell 1976) of a small fetus associated with either a loss of growth support (low diastolic flow velocity, high uterine artery resistance, low uteroplacental bed perfusion) or low growth potential (normal uterine artery flow velocity waveforms). This question may be clarified by relating uterine artery waveforms to patterns of ultrasound growth.

The relation between uteroplacental and umbilical placental arterial waveforms is interesting. Fetal growth retardation with very low uterine artery diastolic flow velocities was associated with low umbilical artery diastolic flow. In pregnancies with abnormal uterine waveforms but a normal umbilical pattern presumably the placental microvascular lesion associated with an abnormal umbilical waveform (Trudinger *et al.* 1983; Giles *et al.* 1985) had not yet fully developed. It is noteworthy that placental nutrition is from the maternal circulation. Normal uterine waveforms and fetal growth retardation suggest a primarily fetal cause. In ovine pregnancy normally both circulations demonstrate a progressive rise in blood flow due to a gradual decrease in vascular resistance rather than an increase in the pressure gradient across them (Dawes 1968*b*; Rudolph & Heymann 1970). Embolization of the uterine circulation (Creasy *et al.* 1972) results in an increase in resistance and reduction in flow in both the uterine and umbilical sides of the placenta (Clapp *et al.* 1980, 1982). This is associated with a reduction in fetal growth rate in the absence of a fall in fetal Po_2, metabolic acidosis or fetal pressor response.

In this series there were 12 patients with severe hypertension and in nine the uteroplacental bed perfusion resistance was high. Severe proteinuric hypertension in pregnancy has been associated with vasospasm, and a reduction in uterine perfusion has been postulated. Our findings would support this. In three patients with a normal velocity waveform it is suggested that the 'hyper-

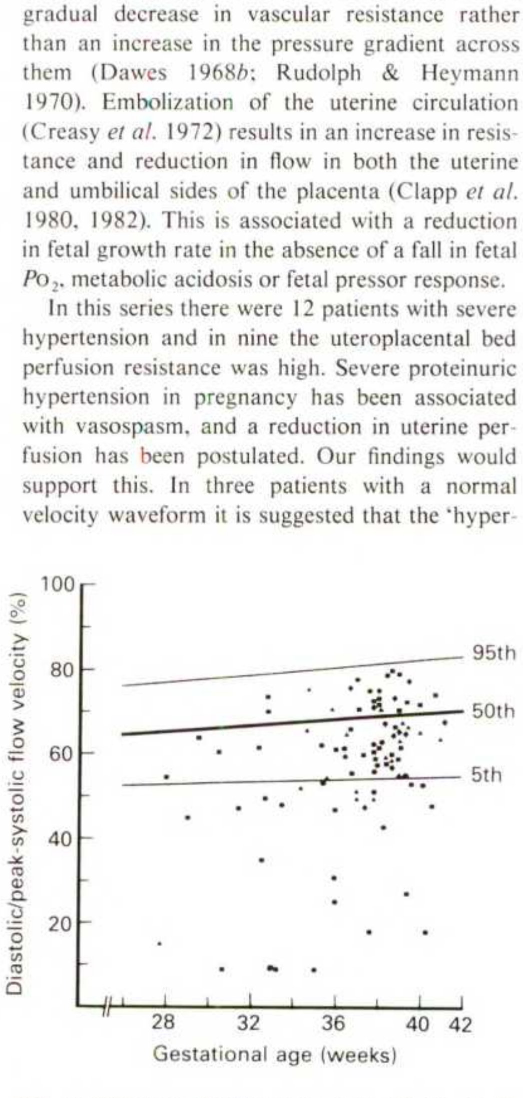

Fig. 6. Antenatal uterine artery flow velocity in 91 complicated pregnancies (normal centile range indicated) related to centile birthweight (● <10th; ▲ 10th–25th; ■ 25th–75th; ◆ >75th).

tensive state' had not yet led to severe vasospasm and uteroplacental flow reduction. If such is the case then these studies can be expected to provide a clinically useful guide to the severity of reduced uterine perfusion in hypertensive disease of pregnancy and the effect of medical therapy which may be used to control maternal disease and delay delivery. Severe maternal hypertension generally leads to early delivery. In only two patients were the fetal umbilical–placental waveforms abnormal and it is presumed that an effect on the fetal side had not yet occurred in association with maternal vasospasm. Serial studies in patients developing hypertension will clarify this point. It is interesting that in experimental renal hypertension in rats (Karlsson *et al.* 1982) a reduction in uterine blood flow was not associated with a reduction in fetal weight and overcapacity or reserve of uteroplacental perfusion was postulated to account for this surprise finding.

Acknowledgments

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Growth of total intrauterine, intra-amniotic and placental volume in normal singleton pregnancy measured by ultrasound

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Summary. The growth of total intrauterine, intra-amniotic and placental volume during the latter half of pregnancy was studied longitudinally with ultrasound in 115 healthy women with normal singleton pregnancies. A parallel planimetric area method was used. The range and distribution of normal values between 20 and 40 weeks was determined for a main study group of 103 primiparous women with which values from 12 parous women were compared. Total intrauterine volume increased from a median of 1006 ml to 4420 ml, intra-amniotic volume from 716 ml to 3406 ml and placental volume, calculated as the difference between total intrauterine and intra-amniotic volume, increased from 259 ml to 801 ml. Variation between individuals was wide at all stages of pregnancy. No significant difference was found between primiparous and parous women. Between successive 5-week periods from 20 to 40 weeks there was evidence that women tended to maintain their initial volume ranking. During the 30–35 week period, rate of growth of total intrauterine and intra-amniotic volume was somewhat faster than the near constant mean rate at other times, while the rate of growth of placental volume decreased after 30 weeks towards term.

Volumetric growth of the pregnant uterus has not been extensively investigated in man. While uterine volume changes appear closely linked to the timing of labour and onset of delivery in laboratory animals (Csapo & Lloyd-Jacob 1963), it has also been suggested that a rise of uterine volume influences uterine activity in the pregnant woman (Csapo *et al.* 1963). Conditions of increased uterine volume, such as acute hydramnios and multiple pregnancy, are associated with preterm labour. Conversely, in cases of fetal growth retardation placental size is reduced (Scott & Jordan 1972) and amniotic fluid volume diminished (Wladimiroff 1980). Volume changes may, therefore, reflect pathological events in pregnancy. At the same time they are an expression of normal growth of the pregnancy amenable to measurement with ultrasound. Using a parallel planimetric area method (Geirsson *et al.* 1982, 1984), the growth of total intrauterine volume (IUV), intra-amniotic volume (IAV) and placental volume (PLAV) was studied longitudinally in the latter half of pregnancy in 103 primiparous and 12 parous healthy women with uncomplicated pregnancies. The objects of the study were to obtain normal values for the growth of these volume spaces and to investigate rates and patterns of volumetric growth.

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Patients and methods

A total of 147 healthy white European women presenting before 20 weeks gestation with a singleton pregnancy were recruited from the antenatal booking clinic. Of these 132 were in their first pregnancy (primiparous group) while 15 were parous women (parous group). In selecting women the only requirement was that they were healthy before the pregnancy and at the time of booking, but no account was taken of maternal body characteristics, smoking habits or social class. Informed consent was obtained in each case. Thirty-two women were subsequently excluded for the following reasons (numbers in parentheses): early or mid-trimester abortion (5), termination (1), chronic hypertension or late-onset severe proteinuric hypertension (5), antepartum haemorrhage (4), pyelonephritis (2), delivery before 35 completed weeks (5) and the required minimum of four examinations was not achieved (10). A mild pregnancy-induced rise of blood pressure towards term (diastolic blood pressure 90–99 mmHg) with or without dependent oedema, but without proteinuria, was not considered a reason for exclusion.

Results from the remaining 115 women with uncomplicated pregnancies, 103 primiparous and 12 parous, were analysed. Mean age for the primiparous was 24 years (range 17–32) and for the parous women 27 years (range 23–36). Mean height for the whole group was 161 cm (range 145–177 cm) and mean midpregnancy weight 62 kg (range 46–98 kg). The mean length of gestation was 40 2 weeks (range 35–42). Women in whom spontaneous labour had not occurred by 42 completed weeks were induced. The mean birthweight was 3331 g (range 2460–4290 g) and the mean corrected birthweight (Altman & Coles 1980) was at the 47th centile (range 3rd–98th centile). All infants were healthy.

Gestational age was determined from the date of the first day of the last menstrual period (LMP) where reliable, and by ultrasound measurements of fetal crown–rump length and fetal biparietal diameter (Campbell & Newman 1971; Sabbagha & Hughey 1978; Christie 1981). Gestational age was adjusted to fit with mean ultrasound values where the crown–rump length differed by more than ±6 days and the biparietal diameter by more than ±9 days from the gestation calculated from the LMP. A crown–rump length measurement was available in 70 women. In addition one or more biparietal diameter measurements were done in all women at or before 20 weeks gestation.

Volume measurements were carried out by one of us (R.T.G.) with a Philips Diagnost B62 Scanner with greyscale and motorized survey/distance system (calibrated velocity 1540 m/s) linked to a Kretztechnik Data Computer/Light Pen System with a 28×21 cm monitor screen. The measurement technique was the parallel planimetric area method described by us previously which allows measurement of total intrauterine volume, including fetus, placenta and amniotic fluid, and of intra-amniotic volume comprising fetus and amniotic fluid (Geirsson *et al.* 1982, 1984). Each woman attended at least four times for measurements (mean 5, range 4–8 times) including at 18–20 weeks and around 36 weeks. Additional measurements were obtained at 28 and 32 weeks and if possible at 24, 38 and 40 weeks. The times were chosen to coincide with antenatal clinic visits. Measurements were done without reference to previous ones. Total intrauterine volume was measured at each examination and all these measurements (581) were used for analysis. Intra-amniotic volume was measured simultaneously if adequate visualization of the placental chorionic plate was obtained. Analysis of IAV was carried out in all cases where a minimum of four measurements including at 18–20 and 36 weeks were obtained (301 measurements). Placental volume was determined by subtracting IAV from IUV (301 values).

Data were grouped by completed week of gestation ±3 days. The individual curves for IUV, IAV and PLAV were plotted. To facilitate statistical analysis a computer program for interpolation was used to estimate volumes at 20, 25, 30, 35, 38 and 40 weeks from measurements at near-by times if a measurement at the exact date was not available. For example, the value at 30 weeks was calculated from a straight line joining the actual values obtained at 28 and 32 weeks. This allowed standardized dates to be used while retaining close longitudinal reflection of the measured growth curve. Median and centile values, and mean and standard deviation were calculated at these dates. Findings in the parous women (referred to separately) were compared with those from the primiparous group with a two-sample *t*-test. Spearman's rank correlation coefficients were calculated to test whether ranking of volumes at successive times were consistent. To assess growth rates at different times, growth increments were calculated for consecutive 5-week periods. A paired *t*-test was used to test whether differences in growth increment between these periods were significant. We also studied the correlation between rate of growth and volume.

Results

Median and centile values for the three volume entities in the primiparous group are given in Table 1 and shown graphically in Figs 1 and 2. Values of IAV and PLAV at 40 weeks were too few for centile calculation. For comparison the mean and SD values are given in Table 2. There was close similarity between values obtained by centile calculation and values estimated by assuming a normal distribution. During the study period from 20 to 40 weeks gestation IUV, IAV and PLAV increased on average by a multiple of 4 5, 4 8 and 3 1 respectively. Variation around the mean was wide at all gestational lengths.

In the parous group the mean values for IUV were 977 ml (SD 103 ml) at 20 weeks rising to 4108 ml (SD 774 ml) at 38 weeks. This was not significantly different from the primiparous group. The IAV and PLAV measurements obtained from four parous women were between the 3rd and 97th centiles for the primiparous group.

Since values at 40 weeks were only available in one-third of the women, a two-sample *t*-test was used to compare values in women with and without a measurement at this time. No significant difference was found for any of the three volume entities at the earlier study dates. The results at 20–35 or 38 weeks did not appear to be biased by the fact that they were based on women of various ultimate lengths of gestation or frequency of measurements.

Individual curves were plotted for each woman and an impression was gained that women with a high initial intrauterine volume tended to continue towards term with a high volume while those with a low volume at mid-pregnancy continued as such. To assess this effect Spearman's rank correlation coefficients and their significance were determined between successive 5-week periods for all three volumes (Table 3). There was good correlation between adjacent time points indicating consistency of volume level for all three volumes from 20 weeks to 38 weeks. For the 40

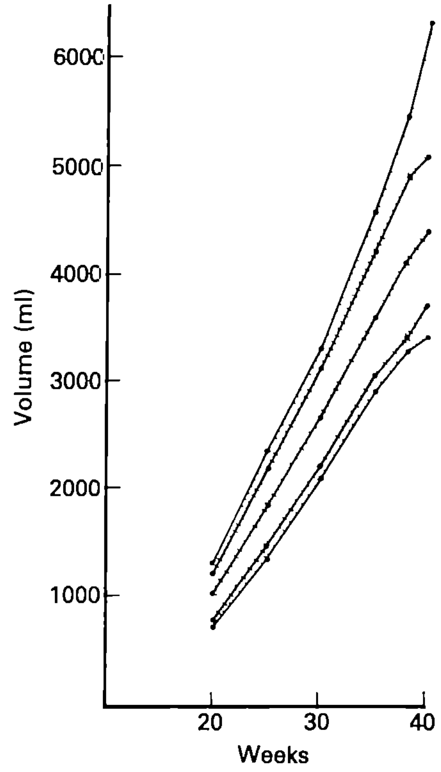

Fig. 1. The median, 3rd, 10th, 90th and 97th centiles of the distribution of total intrauterine volume in primiparous women by gestational age.

Table 1. Median, 3rd and 97th centile values for intrauterine (IUV), intra-amniotic (IAV) and placental volume (PLAV) computed at standardized lengths of gestation in primiparous women

Gestation (weeks)	IUV (ml)			IAV (ml)			PLAV (ml)		
	3rd	Median	97th	3rd	Median	97th	3rd	Median	97th
20	688	1006	1260	472	716	964	113	259	387
25	1348	1823	2348	963	1365	1929	244	436	660
30	2098	2694	3324	1533	2058	2605	363	595	921
35	2927	3620	4606	2238	2888	3547	467	717	1165
38	3295	4137	5505	2581	3289	4025	495	749	1000
40	3457	4420	6338	—*	3406	—*	—*	801	—*

*Number of women studied too small for centile calculation (numbers given in Table 2).

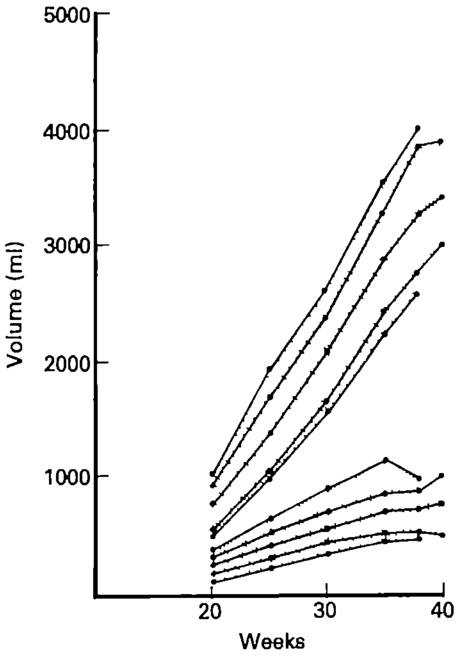

Fig. 2. The median, 3rd, 10th, 90th and 97th centiles of the distribution of intra-amniotic (upper plots) and placental volume (lower plots) in primiparous women by gestational age.

week values, where the number of observations was smaller and with increasing separation of measurement times, the correlations were less strong. Ranking was also evident in the parous group.

Growth increments were calculated for each successive 5-week period (Table 4). For IUV the increment (rate of growth) was similar during the two first and the last period. Volume increment was significantly different only between the 25–30 and 30–35 week periods. There was no significant difference between the primiparous and parous groups. For IAV and PLAV the difference was significant between 25–30 and 30–35 weeks and also between 30–35 and 35–40 weeks. Growth rate was thus somewhat faster between 30–35 weeks than at other times for IUV and IAV. After 30 weeks the growth rate of PLAV continued to fall during the two last 5-week periods. A mean weekly growth rate from 20–40 weeks cannot be given for PLAV but was for IUV 177 ml/week and for IAV 138 ml/week.

To investigate whether there was a correlation between rate of growth and volume, the relation of the increment over a 5-week period to the mid-period value (initial value + final value)/2 was studied (Oldham 1968). The correlation coefficients (Table 5) for IUV and IAV were highest for the 20–25 week period showing that there was a tendency for larger initial volumes to increase faster during this time compared with the smaller initial volumes. This tendency was less pronounced later on in pregnancy. For PLAV the same trend occurred in the 25–30 week period.

Discussion

The values presented on growth of total intrauterine, intra-amniotic and placental volume have been gathered with an ultrasonic scanning method previously shown to have acceptable accuracy (Geirsson *et al.* 1982, 1984). Total intrauterine volume could be measured in all women. Where the placenta was implanted posteriorly the intra-amniotic area could often not be measured towards the end of pregnancy due to shadowing from the fetus. Because of this, measurements of intra-amniotic and placental volume were fewer and derived from pregnancies

Table 2. Mean and SD for intrauterine (IUV), intra-amniotic (IAV) and placental volumes (PLAV) computed at standardized lengths of gestation in primiparous women

Gestation (weeks)	IUV (ml)			IAV (ml)			PLAV (ml)		
	n	Mean	SD	*n*	Mean	SD	*n*	Mean	SD
20	103	990	167	53	718	134	53	255	61
25	103	1834	281	53	1361	231	53	431	83
30	103	2690	344	53	2035	279	53	599	116
35	103	3657	446	53	2858	339	53	724	145
38	76	4157	573	39	3304	413	39	757	128
40	38	4524	720	17	3446	287	17	789	184

Table 3. Spearman's rank correlation coefficients and their significance for total intrauterine (IUV), intra-amniotic (IAV) and placental (PLAV) volumes (primiparous group)

	25 weeks			30 weeks			35 weeks			38 weeks			40 weeks		
Weeks	IUV	IAV	PLAV	IUV	IAV	PLAV	IUV	IAV	PLAV	IUV	IAV	PLAV	IUV	IAV	PLAV
20	0 84	0 85	0 61	0 75	0 76	0 47	0 60	0 62	0 40	0 52	0 59	0 45	0 37*	(0 07)	0 60*
25				0 92	0 92	0 88	0 71	0·71	0 68	0 59	0 55	0 64	0 42	(0 17)	0 74
30							0 84	0 82	0 80	0 72	0 64	0 76	0 62	(0 28)	0 90
35										0 89	0 84	0 90	0 73	(0 42)	0 94
38													0 88	0 61*	0 87
Total no. of observations	103	53	53	103	53	53	103	53	53	76	39	39	38	17	17

*All unmarked figures are significant with $P<0$ 01. Figures marked * were significant with 0 01<$P<0$ 05.
Figures in parentheses were not statistically significant ($P>0$ 05).

Table 4. Growth increments over 5-week periods for total intrauterine (IUV), intra-amniotic (IAV), and placental (PLAV) volumes (primiparous group)

Gestation (weeks)	IUV (ml) Mean	SD	SEM	*n*	IAV (ml) Mean	SD	SEM	*n*	PLAV (ml) Mean	SD	SEM	*n*
20–25	843	165	16	103	643	137	19	53	176	58	8	58
25–30	857	143	14	103	674	123	17	53	168	54	7	53
30–35	967*	239	24	103	823*	182	25	53	125*	71	10	53
35–40	880	471	76	38	612*	290	70	17	31*	87	21	17

*Significantly different increment from preceding period ($P<0.01$, paired *t*-test).

where the placenta was situated anteriorly or laterally in the uterus. All measurements were made by one observer in pregnancies studied longitudinally.

For the construction of growth curves representative of a population a longitudinal study allows close approximation of the true growth curve (Deter *et al.* 1982). The sample size was kept large because of the expected wide spread of values particularly late in pregnancy and to give a comprehensive picture of 'normal' volumetric growth in pregnancy. For this purpose we excluded individuals with recognizable obstetric abnormalities. While the majority of individual growth curves for total intrauterine and intra-amniotic volume showed a linear growth pattern some exhibited either a reduced rate towards term or an increase. Use of interpolation to compute volumes at standardized dates facilitated data analysis and made fewer assumptions about the actual trend of volume than linear regression analysis, which also did not fit the data on placental volume change. Median and centile values were used to construct growth curves since this gives a more accurate reflection of growth if values are not consistent with a normal distribution. The median, 3rd and 97th centile values were, however, similar to the values given by the mean ± 1·9×SD predicted for a normal distribution. Values from the parous women were comparable to the range obtained in the larger primiparous group which, therefore, can be used as representative of normal values in both first and later pregnancies.

The spread of values was large at any stage of pregnancy, with some women having almost twice as much intrauterine volume as others. The SD expressed as a percentage of the mean was for total intrauterine and intra-amniotic volume usually around 14%. The large difference between the smallest and largest volume at any time is consistent with common clinical experience and with findings obtained with the less accurate prolate ellipsoid method. The standard deviation given in the nomogram of Gohari *et al.* (1977) is considerably larger than that shown here while mean values appear similar. Levine *et al.* (1979) report lower mean values but their tolerance limits indicate a similar spread of values. In neither study were individual cases followed longitudinally. Analysing the logarithms of volume measurements resulted in more stable SD values with time but the basically linear appearance of the growth curves was lost.

The mean rate of growth for total intrauterine and intra-amniotic volume remained similar throughout the latter half of pregnancy except for a somewhat steeper rate of increase between 30 and 35 weeks. This was more marked for IAV and may coincide with a period of increased fetal body growth and a larger volume of amniotic fluid than in the period around or after term. It is possible that in some women delivered before 40 weeks, and where a measurement after 36 weeks was not obtained, the rise in volume preceding delivery could have been faster than in those delivered at a later date. This is an area which requires further investigation.

A tendency for women to retain their relative volume level was indicated by the correlation coefficients between successive times. With increasing separation of time points the correlations were weaker, that is the predictability of one measurement on the basis of an earlier one diminished. Therefore a screening procedure in the third trimester designed to be indicative of the pregnancy end-volume would be best carried out after 30 weeks gestation. There was a tendency for women with larger initial IUV and IAV also to show the largest rates of increase, contributing

Table 5. Correlation coefficients for increment/mid-period values for total intrauterine (IUV), intra-amniotic (IAV), and placental (PLAV) volumes (primiparous group)

Compared weeks	IUV		IAV		PLAV	
	r	*n*	*r*	*n*	*r*	*n*
20–25	0.72	103	0.74	53	0.42	53
25–30	0.45	103	0.40	53	0.61	53
30–35	0.44	103	0.34	53	0.42	53
35–40	0.54	38	−0.004	17	−0.11	17

to a general increase in the variability with time.

The rate of placental volume growth gradually diminished after about 30 weeks. This is consistent with the findings of Bleker *et al.* (1977) who, using a similar scanning method for measuring anterior placentas in a longitudinal study of 12 women, found that the maximum volume was reached between 28 and 36 weeks in nearly all. We calculated placental volume indirectly from the difference between total intrauterine and intra-amniotic volumes, which because of their spherical form, are easier to measure accurately than the placenta itself. Variation in placental volume was large at any stage of pregnancy (SD 20% of mean). The rate of growth decreased gradually so that in the last 5-week period the mean rate was under one-fifth of the growth rate between 20 and 25 weeks. This is consistent with the results of Hellman *et al.* (1970), who found in a cross-sectional ultrasonic study, with a method involving approximation of placental volume, that the time taken for the placenta to double its volume was 4.75 times longer towards the end of pregnancy than in or before mid-pregnancy. Volumetric growth of the pregnancy during the third trimester is thus primarily due to an increase of fetal size and to some extent of amniotic fluid. The placenta appears to continue to provide adequately for the fetus till term in spite of little increase in its size.

As an approach to growth of the fetoplacental unit, measurements of intrauterine volume changes are of value in describing normal physiology. We are currently investigating to what extent they contribute to the diagnosis of disturbed fetal growth or health.

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Gastroschisis and exomphalos: precise diagnosis by midpregnancy ultrasound

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Summary. As part of a regional screening programme for neural-tube defects the cause of the raised α-fetoprotein levels was correctly identified in 13 pregnancies with a fetal abdominal wall defect by the 22nd week. Careful ultrasound study identified gastroschisis in seven fetuses and exomphalos in six: the presence or absence of a sac, the course of the umbilical vessels and the abdominal organs involved were the most important diagnostic criteria. Pregnancy continued into the third trimester in five cases complicated solely by gastroschisis and two babies have survived the neonatal period following surgical correction. It is suggested that precise identification by ultrasound of the type and severity of abdominal wall defect and also of the presence or absence of associated anomalies will enable the selection of some babies with gastroschisis or isolated exomphalos which have a good prognosis for survival without handicap.

Soon after the introduction of prenatal diagnosis of neural-tube defect (NTD) by the finding of elevated amniotic fluid α-fetoprotein (AFP) concentration, it became clear that other fetal abnormalities, such as abdominal wall defect (AWD), would also be identified (Leeschat & Treffers 1975). Biochemical testing of amniotic fluid cannot reliably differentiate between NTD and AWD, and the diagnosis of AWD may be made at the time of pregnancy termination only. However, the combination of biochemical testing and detailed ultrasound scanning enables a more precise identification of the abnormality to be made before the parents are counselled and a decision regarding termination is made.

This decision may be much more difficult for parents if the fetus has an AWD because, in contrast to NTD, there is a reasonable chance of survival without handicap if surgical repair in the early neonatal period is successful. Nevertheless, prognosis depends on a number of factors of which the most important are the nature of the AWD (whether exomphalos or gastroschisis) and the presence or absence of additional anomalies. Several authors have reported a survival rate of 80–90% in babies with gastroschisis, which is very rarely accompanied by non-alimentary anomalies (Grosfeld *et al.* 1981; King *et al.* 1980; Mayer *et al.* 1980); this contrasts with the much worse prognosis for exomphalos, in which there is a high incidence of other anomalies, aneuploidy and congenital heart disease being particularly common.

Ultrasound assessment can be of value not only in helping to differentiate exomphalos from gastroschisis, but also in defining whether the fetus is otherwise normal.

Subjects and methods

The ultrasound unit at the Queen Mother's Hospital, Glasgow, acts as a referral centre for hospitals in the West of Scotland, all of which offer maternal serum AFP screening. Some patients with elevated AFP, including those

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booked for delivery at the Queen Mother's Hospital, have detailed ultrasound scanning in our department before amniocentesis, which may then be omitted if a fetal abnormality is confidently diagnosed. Other patients have amniocentesis performed in the referring hospitals and may be referred for confirmation of the presence of fetal deformity or for clarification if the amniocentesis results are equivocal (usually elevated amniotic fluid AFP with a single cholinesterase band).

If an AWD is identified, we attempt to describe precisely the type of defect and those fetal organs which have herniated. The presence of a sac, the point of entry of the umbilical vessels and the abdominal organs involved are the three most important diagnostic features.

Gastroschisis has no sac and the umbilical vessels enter the abdominal wall normally, adjacent to the defect (Fig. 1). In most cases only small or large bowel or both are extruded, although other organs (e.g. stomach and internal genitalia) may be involved. The liver is always normally situated. In addition, we have noted a characteristic cauliflower-like appearance of the herniated bowel, which in mid-pregnancy seems to be present in a single mass (Fig. 2) and not in the form of individual loops which may be seen in the third trimester. A further ultrasound feature of particular diagnostic importance is that the mass of bowel may lie at some distance from the fetal abdominal wall and, indeed, no connection may be seen between the two. The mass may be seen floating freely in the amniotic fluid or adjacent to the fetal limbs. For this reason, it is mandatory to scan the entire uterine cavity carefully in these cases, even when the fetal abdominal wall appears normal.

The findings in exomphalos range from a small sac containing a knuckle of bowel or omentum (Fig. 3) to complete disruption of the structure of the fetal body which makes orientation in standard longitudinal and transverse sections of the fetus difficult. A sac is always present initially, but it may be difficult to identify in large lesions if it lies in contact with the amnion over a large part of its surface. The insertion of the umbilical cord may be seen at some point on the sac but the vessels cannot usually be seen entering the fetal body. The absence of any free umbilical cord is an important diagnostic feature in body stalk anomaly.

The other fetal organ systems (particularly the fetal heart) are also carefully studied to identify additional anomalies. Because, in our practice, the fetal karyotype is determined in every mid-pregnancy sample of amniotic fluid taken for prenatal diagnosis, a second amniocentesis is not necessary for this purpose.

When all this information is available the parents are counselled, usually by the obstetrician who has undertaken the scanning. When gastroschisis is the likely diagnosis, we stress the magnitude of the neontal surgical problem and associated intensive care, but state that other malformations are unlikely and that, if the child survives, its development should be normal. However, when exomphalos is the diagnosis we take into account which organs lie outside the fetus in describing the likely surgical problems and stress that other anomalies commonly accompany this condition.

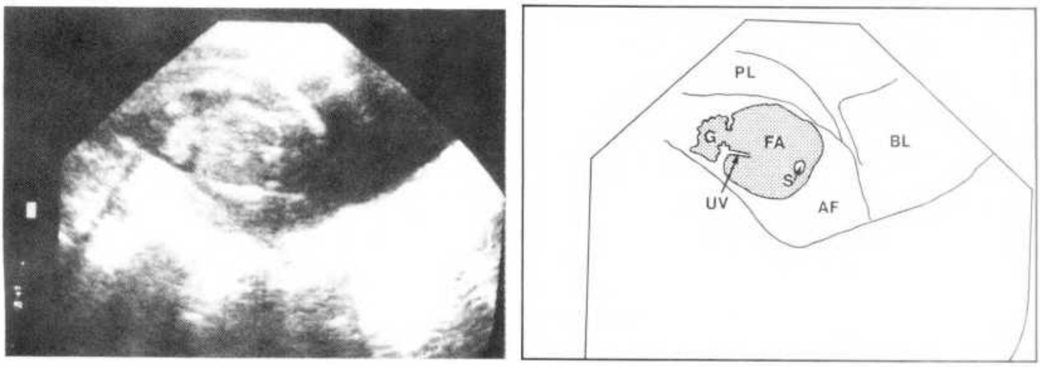

Fig. 1. Gastroschisis. A transverse section through the fetal abdomen (FA). The spine (S) is at 3 o'clock and the umbilical vein (UV) is seen entering the abdomen just below the gastroschisis (G), which has no sac. AF, amniotic fluid; PL, placenta; BL, maternal bladder.

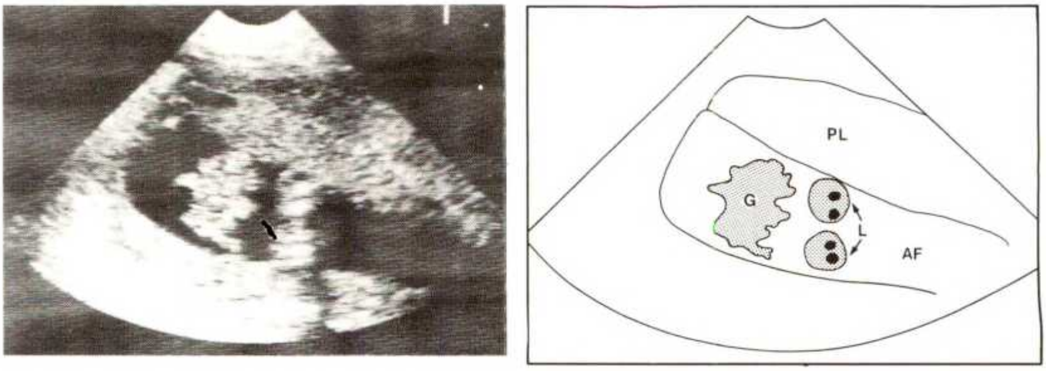

Fig. 2. Gastroschisis. The scanning plane is below the fetal buttocks. To the right is a transverse section of both legs below the knee (L) and to the left is the characteristic cauliflower-like gastroschisis (G). AF, amniotic fluid; PL, placenta.

Results

Between January 1982 and July 1983, as part of the regional AFP screening programme, detailed ultrasound scanning was performed in 53 singleton pregnancies in which the presence of fetal abnormality seemed likely (Fig. 4). In 42 of the 53, amniocentesis had been performed because of elevated serum AFP, and the amniotic fluid AFP concentration found to be elevated (the upper limit of normal varying between 3·0 and 3·5 multiples of the median at differing gestational ages). In the remaining 11, serum AFP was elevated but a lesion (NTD or AWD) was identified with ultrasound before planned amniocentesis, which was not therefore performed.

An NTD was identified in 29 of the 53 pregnancies, and all were terminated. In 11 pregnancies with elevated amniotic fluid AFP, prolonged (and usually repeated) scanning identified no abnormality of the fetus. All these pregnancies continued and the normality of the fetus was confirmed at the time of delivery.

In the remaining 13 pregnancies an AWD was identified. Amniotic fluid AFP was elevated in 10 out of the 11 patients who had an amniocentesis. Table 1 summarizes the biochemical, ultrasound and pathological features of these pregnancies, which include three with coexisting AWD and NTD. The type of AWD seen was exomphalos in six pregnancies, including all three with coexistent NTD. An additional major anomaly was identified in two other fetuses with a large exomphalos (trisomy 18 in one, and the other a closed spinal deformity which was a component of a body stalk syndrome). These five pregnancies, which were associated with a large exomphalos and an additional problem, were terminated and the sixth, associated with a small exomphalos, aborted spontaneously at 22 weeks.

The remaining seven fetuses had gastroschisis

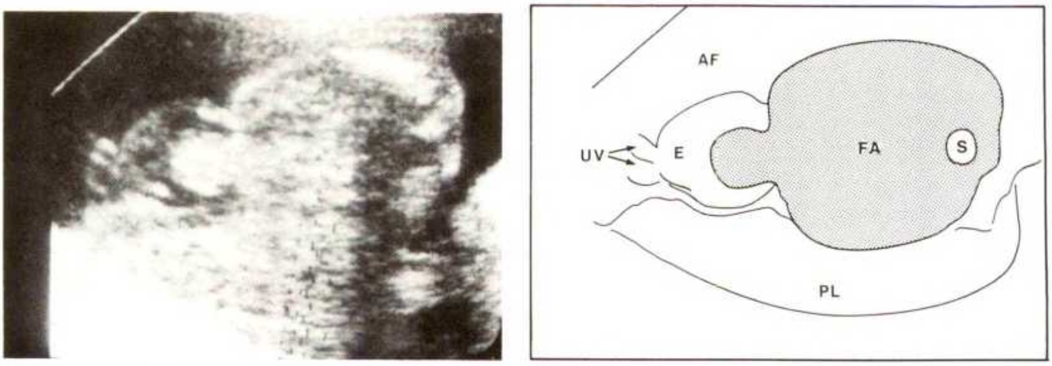

Fig. 3. Small exomphalos. A transverse section through the fetal abdomen (FA). The spine (S) is at 3 o'clock and the exomphalos (E) with its sac containing a knuckle of bowel is on the left. The umbilical vessels (UV) are clearly seen at the apex of the sac. AF, amniotic fluid; PL, placenta.

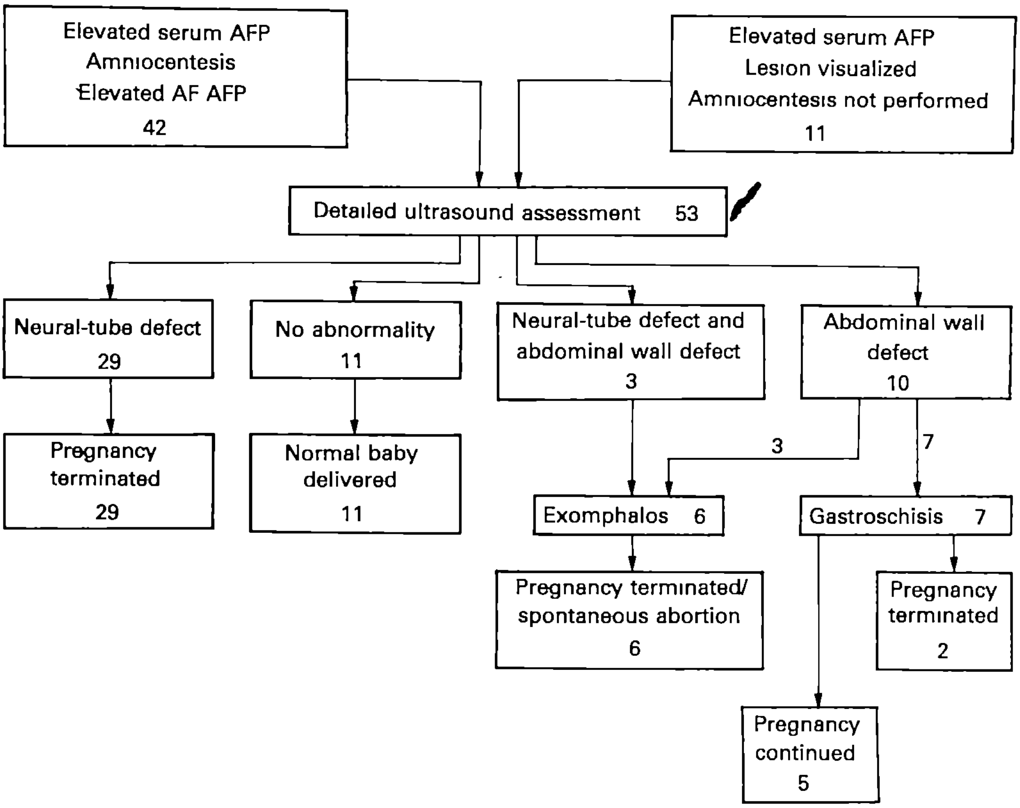

Fig. 4. The source, findings and outcome of the detailed ultrasound assessment in 53 singleton pregnancies.

and no other abnormality identified, and after counselling, two of the seven pregnancies were terminated at the parents' request. The remaining five pregnancies continued into the third trimester and the booked deliveries were transferred to our hospital, which is adjacent to the Regional Neonatal Surgical Unit. The neonatal paediatrician and paediatric surgeon were forewarned and consulted the parents. Three of the babies were delivered by elective caesarean section (intending to minimize trauma and infection of the exposed bowel), and two were delivered spontaneously at 33 and 34 weeks gestation.

Successful surgical repair of the gastroschisis was performed in all five babies, but three died of different and unexpected postoperative complications (hyaline membrane disease and pulmonary haemorrhage; superior vena caval thrombosis and intussusception of an ileal anastomosis; wound dehiscence requiring resuture, small bowel fistula and septicaemia in the third).

Discussion

Although the incidence of AWD is generally low compared with that of NTD, it was present in almost 25% of the babies in this series. While this is merely a reflection of an uneven pattern of referral, it may not be untypical of the workload of other referral ultrasound units. The ratio of AWD to NTD may well be rising as the absolute incidence of NTD is believed to be falling (Leck 1983).

Amniotic fluid testing cannot discriminate between AWD and NTD, although an extremely high level of AFP combined with either a single cholinesterase band or an atypical second band seems strongly suggestive of AWD. The suggestion that specific cells can be identified cytologically in amniotic fluid from pregnancies with AWD or NTD (Godsen & Brock 1978) has not been confirmed. Although our own practice is to confirm the presence of NTD with ultrasound before termination of pregnancy even in preg-

Table 1. Biochemical, ultrasonic and pathological findings, with outcome, in 13 pregnancies associated with an abdominal wall defect

	Amniotic fluid				
Patient no.	AFP (in MOM)	Cholinesterase banding	Ultrasound diagnosis	Pathological diagnosis	Outcome
1	28	1	Gastroschisis	Gastroschisis	Elective LSCS. Surgical repair, infant had wound dehiscence and septicaemia, died day 7
2	33	1	Gastroschisis	Gastroschisis	SVD at 33 weeks Surgical repair, infant had hyaline membrane disease, died day 3
3	32	1+1*	Gastroschisis	Gastroschisis; ileal stenosis; syndactyly	Elective LSCS. Surgical repair with local resection, had superior vena caval thrombosis, died day 33
4	18	2	Gastroschisis	Gastroschisis	Pregnancy terminated
5	34	1+1*	Gastroschisis	Gastroschisis	SVD at 34 weeks. Surgical repair, infant survived
6	0.5†	1	Small exomphalos	Small exomphalos	Spontaneous abortion at 22 weeks
7	—	—	Large exomphalos; spina bifida; hydrocephalus	Large exomphalos; spina bifida; hydrocephalus	Pregnancy terminated
8	22	2	Large exomphalos; spina bifida	Large exomphalos; spina bifida	Pregnancy terminated
9	111	2	Large exomphalos	Large exomphalos, trisomy 18	Pregnancy terminated
10	8	1+1*	Large exomphalos; closed spinal deformity; ? body stalk syndrome	Body stalk syndrome; large exomphalos; kyphoscoliosis; short umbilical cord; single umbilical artery	Pregnancy terminated
11	57	2	Gastroschisis	Gastroschisis	Pregnancy terminated
12	44	2	Gastroschisis	Gastroschisis	LSCS in labour at 36 weeks. Surgical repair, infant survived
13	—	—	Large exomphalos; anencephaly; spina bifida	Large exomphalos; anencephaly; complete spina bifida, single umbilical artery	Pegnancy terminated

* Second cholinesterase band but different velocity to that seen with NTD.

† Amniocentesis performed after ultrasonic diagnosis of exomphalos in a patient with elevated serum AFP.

MOM, Multiples of the median.

nancies with apparently unequivocal biochemical results (elevated amniotic fluid AFP and two cholinesterase bands), we feel it is especially important in those pregnancies with equivocal results (borderline raised amniotic fluid AFP, raised AFP with single or atypical second cholinesterase band). In 11 of our patients, this policy enabled us to reassure the parents that the fetus was normal. In the 13 in which an AWD was identified, we considered that only the most complete and accurate information about the condition of the fetus, and the prognosis that this carried, would enable the parents to reach the best decision.

Detailed ultrasound scanning enabled a correct diagnosis to be made of the presence and type of fetal abnormality in all of these patients. Although no significant fetal malformations in association with AWD were overlooked, there was no case of congenital heart disease in this small series, and the strong association between exomphalos and congenital heart disease (which can be difficult to identify ultrasonically), compared with its rarity in the presence of gastroschisis, is one of our reasons for counselling parents in more guarded terms when the former condition has been recognized. In the only pregnancy with exomphalos without associated anomalies (patient 6) the parents planned to continue the pregnancy, but spontaneous abortion occurred.

In five cases in which the fetus had gastroschisis, the parents elected to continue the pregnancy. Despite arranging delivery with neonatal intensive care and surgical facilities at hand, and elective caesarean section in three patients, only two of the five infants born survived the neonatal period. However, the three babies that died each suffered very uncommon and different postoperative complications, and this rather disappointing outcome does not negate the principle of accurate prenatal diagnosis as a prelude to informed counselling.

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Baseline fetal heart rates from 15 to 38 weeks gestation in normotensive and hypertensive pregnancies

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Summary. To determine whether the fetal heart behaves differently in normotensive and hypertensive pregnancies, the changes in baseline fetal heart rate were investigated prospectively from 15 to 38 weeks gestation in 16 women who were normotensive at the time of booking in the antenatal clinic. Fetal heart rate recordings were made ultrasonically, and were computer-processed by the programs TELEPLOT and BASELINE. Those women who remained normotensive exhibited a decrease of fetal heart rate with advancing gestational age, but this did not occur in the six women who eventually developed hypertension.

In a previous study, Dalton & Shepherd (1982) investigated fetal heart rate with particular reference to maternal hypertension. They found a relative tachycardia during the third trimester in hypertensive pregnancies, and indeed this appeared to be present before the maternal blood pressure became abnormal. Two alternative hypotheses were put forward: either the tachycardia was a consistent response to a failing placenta, or it was a transient response to abdominal palpation or to maternal anxiety in attending the clinic. However, the methodology of their study was such that much longer periods of observation were needed to determine whether the tachycardia observed was transient, or at which gestational age it became apparent.

In order to determine whether the behaviour of the fetal heart is indeed different in hypertensive pregnancies, we have prospectively investigated the effect of gestational age on baseline fetal heart from 15 to 38 weeks gestation in nulliparous women who were normotensive at the time of booking in the antenatal clinic. This has been part of our ongoing study into the effects of maternal hypertension on the fetal cardiovascular system. We have reason to believe that the behaviour of the fetal heart outwith the range 15 to 38 weeks is qualitatively different to that within this range, and this is to be the subject of a separate report.

Subjects and methods

Sixteen women were selected randomly at their first antenatal clinic visit. The only criteria for inclusion in the study were that they were nulliparous, had a booking blood pressure of <140/90 mmHg, and had no previous history of hypertension. Their ages ranged from 19 to 30 years, and they were all in good health. Their gestational ages were confirmed by ultrasound scan.

Fetal heart rate recordings of 30 min duration were made at intervals of 3–4 weeks from the first visit (mean 15·8 weeks, range 11–20 weeks) until delivery (mean 39 6 weeks, range 38–43 weeks). All recordings were made with the mother lying in the left lateral semirecumbent position, and abdominal palpation was *not* performed. At the end of each recording session, maternal blood pressure was taken using a conventional mercury

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manometer, with the mother sitting upright. Diastolic pressures were taken at Korotkoff IV.

The fetal heart beat was detected with ultrasound, using either a Sonicaid D205 fetal heart detector (up to 27 weeks) or a Hewlett Packard 8030 fetal heart monitor (from 28 weeks onwards), and the signals were fed into an HP 9825 or HTP 9826 computer running the HPL program TELEPLOT. Fetal heart rates were calculated in real-time over epochs of 3750 ms, and were stored on computer disc for subsequent processing by the HPL program BASELINE, which calculated the average baseline fetal heart rate for each recording. Detailed accounts of our system and of the programs TELEPLOT and BASELINE are given elsewhere (Dalton *et al.* 1984; Dalton & Dawson 1984). On occasions, the amplitude-dependent audiosignal preprocessor of the original TELEPLOT system was replaced by a frequency-dependent preprocessor (Manning *et al.* 1983).

After delivery, the mothers were classified as normotensives or hypertensives depending on their blood pressures recorded at any time during the pregnancy, in labour, or in the first 24 h after delivery. Hypertensives were defined as those with blood pressures of either 140/90 mmHg on at least two occasions 24 h apart, or 160/110 mmHg on at least two occasions 15 min apart.

Statistical analysis of the results were performed using SPSS, the Statistical Package for the Social Sciences. Analysis of variance was performed using epochs of 4-weeks gestational age. It is important to note that the initial dataset was of unbalanced form because occasionally two observations were performed on individual women within a single 4-week epoch of gestational age, and because not all patients were equally represented at all phases of the study. There was also the possibility of a disproportionate influence of one or more individual pregnancies on the overall dataset. However, although these factors presented a potential source of statistical bias, matrix algebra techniques used in the SPSS implementation of the analysis of variance allowed any such bias to be eliminated.

Results

All 16 women were delivered of live healthy babies, whose weights were within the normal range. Ten women remained normotensive (mean age 25·1 years, range 19–30 years), and six became hypertensive (mean age 24·2 years, range 22–30 years). In total, 127 recordings were made: 77 in the sustained-normotensives and 50 in the eventual-hypertensives.

Fail times were calculated for each fetal heart rate recording. Fig. 1 shows the average fail times associated with our recording method in the range 15–38 weeks gestation. 'Raw' fail-time (62% overall) was defined as the proportion of real-time which contained erroneous or doubtful cardiac intervals, as determined by the error-detection algorithm in TELEPLOT. 'Interpolated' fail time (41% overall) was the proportion of real-time which could not be interpreted despite operation of the error-reduction algorithm. 'Corrected' fail-time (33% overall) was the proportion of 3750 ms intervals during which no reliable estimate of fetal heart rate could be made.

In Fig. 2, the average fetal heart rates of the sustained-normotensives and the eventual-hypertensives are considered separately for the second and third trimesters, within the range 15–38 weeks. In the sustained-normotensives, the fetal heart rate decreased from 148 to 142 beats/min ($P<0\ 005$), whereas in the eventual-hypertensives the fetal heart rate remained unchanged at 145 beats/min.

Fig. 3 shows the fetal heart rates at each individual recording session plotted against gestational age in those pregnancies which remained normotensive (Fig. 3*a*) or became hypertensive (Fig. 3*b*). In the sustained-normotensives there was a clear and highly significant fall in the average fetal heart rate of around 0·5 beats/min per week over the period 15–38 weeks ($F = 9{\cdot}40$; d.f. = 5 62; $P<0{\cdot}001$). In the eventual-hypertensives, on the other hand, there was no significant change in the average fetal heart rate over this period.

Discussion

We have shown, in 16 initially normotensive pregnancies, that there is a difference in behaviour of the fetal heart between mothers who remain normotensive and those who become hypertensive. Over the range 15–38 weeks, the fetal heart rate decreases with gestational age in the sustained-normotensives (by around 0·5 beats/min/week on average), but in the eventual-hypertensives it does not. This may reflect fetal adaptation to a failing placenta in those mothers who become hypertensive during the pregnancy, but it remains to be seen how the fetal heart rate behaves in chronically hypertensive mothers.

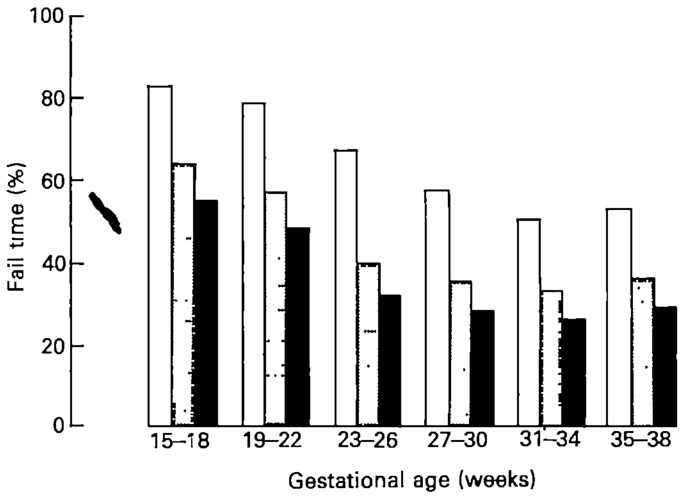

Fig. 1. Averages of raw fail times (☐), interpolated fail times (▨) and corrected fail times (■) for fetal heart rate recordings made at each epoch of gestational age. Definitions of fail times are given in the text.

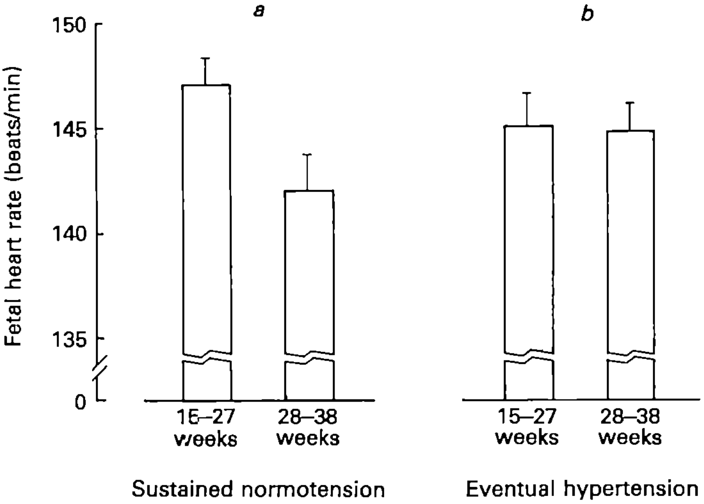

Fig. 2. Average fetal heart rates in the second and third trimesters (within the range 15–38 weeks): (*a*) in those pregnancies which remained normotensive, and (*b*) in those which eventually became hypertensive. Standard error bars are shown.

It is only in those women who remained normotensive that our observations confirm the work of Ibarro-Polo *et al.* (1972) and of Schifferli & Caldeyro-Barcia (1973), who described a decrease of fetal heart rate with advancing gestational age using less precise measuring techniques than ours.

The reason for the fall in fetal heart rate in sustained-normotensives is uncertain. Schifferli & Caldeyro-Barcia (1973) have suggested that it may be due to the development of increasing parasympathetic tone, but the results of their atropine experiments must be interpreted with caution, as they gave the atropine to the mother rather than to the fetus. Furthermore, there is no evidence that the human fetal parasympathetic

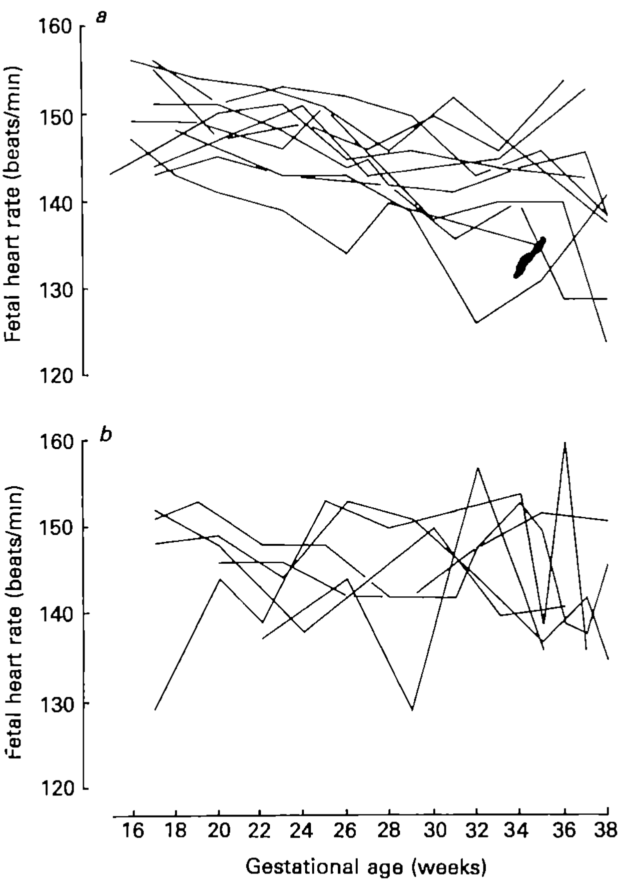

Fig. 3. Baseline fetal heart rates for each fetus at each individual recording session, plotted against gestational age: (*a*) in those pregnancies which remained normotensive, and (*b*) in those which eventually became hypertensive.

system is developed as early as their hypothesis would demand. A more likely explanation for the decreasing fetal heart rate with advancing gestational age is that it is mediated through adrenal catecholamines, and there are several lines of indirect evidence for this. First, there is experimental evidence that the human fetal adrenal gland becomes particularly well developed from 14 weeks onwards (Carr & Casey 1982). Second, it is already well established that there is an age-related reduction of catecholamine supersensitivity in the fetus (Dawes 1974). Third, there is recent experimental evidence to suggest that the fetus is subject to a resting cardio-acceleratory drive which diminishes with advancing gestational age (despite the contemporaneous increasing development of the autonomic nervous system), and which can be pharmacologically blocked (Dalton *et al.* 1983). Nevertheless, when discussing fetal heart rate, it is important to remember not only that the autonomic nervous system probably develops relatively late in gestation, but also that our understanding of its development in the human fetus is particularly sketchy. Even in the fetal lamb, where autonomic development is certainly better understood, much still remains controversial (Dalton *et al.* 1983).

The situation is even less clear in fetuses of hypertensive mothers. In an entirely different series of pregnancies, Dalton & Shepherd (1982) found preliminary evidence that the fetal heart rate is higher in hypertensives in late pregnancy, although 74% of their recordings were from 36 weeks gestation onwards. Thus their results are not directly comparable with ours, given our recording range (for this report) of 15–38 weeks gestation. Nevertheless, if we may assume that in very early pregnancy the fetal heart rates are similar in both sustained-normotensives and eventual-hypertensives, then it follows that the fetal heart rate must go through an intermediate phase where it begins to behave differently in the two groups, well before the definitive fetal tachycardia of maternal hypertension is achieved in later pregnancy. Our results show that between 15 and 38 weeks gestation the fetal heart does indeed behave differently in the sustained-normotensives and the eventual-hypertensives.

Adrenal catecholamines may well modulate this difference in behaviour, as was more fully argued elsewhere (Dalton & Shepherd 1982). Indeed, the two groups of fetuses may well run at different catecholamine levels, as also appears to be the case with growth-retarded fetuses (Divers *et al.* 1981).

The 37% incidence of hypertension in our series (i.e. six women out of 16) was not significantly in excess of the 32% incidence of hypertension which Dalton & Newcombe (1984) found in the overall population of nulliparous singleton Cardiff residents delivered in the decade 1970–1979 (i.e. 4546 women out of 16 340; $\chi^2 = 0{\cdot}34$; d.f. = 1; NS).

Acknowledgments

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Progesterone, cortisol and oestradiol-17β in the initiation of human parturition: partitioning between free and bound hormone in plasma

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Summary. The concentrations of total and free progesterone, oestradiol-17β, and cortisol were measured in the plasma of 24 pregnant women from 10–17 days prepartum, during labour, and for 2–3 days postpartum. All the women were delivered vaginally, and their hormonal profiles were similar, whether they initiated labour spontaneously ($n=11$) or were induced by rupture of the fetal membranes ($n=13$). Before labour, the plasma concentrations of total radioimmunoassayable progesterone, oestradiol-17β and cortisol were 557·3 (SEM 70 3) nmol/l and 590·0 (SEM 76·7) nmol/l, 94 3 (SEM 18·7) nmol/l and 111·6 (SEM 19 8) nmol/l, and 1087·2 (SEM 103 7) nmol/l and 1020·7 (SEM 100·7) nmol/l, for the spontaneous and induced groups, respectively. During labour progesterone and oestradiol-17β declined in maternal plasma to around 130 nmol/l and 30 nmol/l in both groups by the end of the third stage. The free fractions of progesterone and oestradiol-17β remained constant throughout labour and over the entire study period at 2–3% and 1–2%, respectively. Total plasma cortisol rose to 1243·7 (SEM 83·3) nmol/l ($P<0{\cdot}02$, spontaneous group) and 1247·5 (SEM 97·4) nmol/l ($P<0{\cdot}001$, induced group) by the end of the first stage of labour. Concomitantly, free cortisol increased from 4·5–5·5% to 7·2–8·2% over this period so that its concentration increased by approximately 2·5-fold in both groups of women during labour. We conclude that the total and physiologically-active free concentrations of progesterone and oestradiol-17β in maternal plasma do not change immediately before the onset of labour. That is, the onset of human parturition does not involve 'progesterone withdrawal' or 'oestrogen augmentation' in peripheral plasma. Total and free concentrations of cortisol are elevated in maternal plasma during labour possibly due to maternal stress.

The withdrawal of the inhibitory effect of progesterone on the pregnant myometrium has been postulated for many years to be a prerequisite for the onset of labour in women (Csapo 1961; Csapo *et al.* 1971). However, despite the efforts of a number of investigators (Eton & Short 1960; Greig *et al.* 1962; Tulchinsky *et al.* 1972; Shaaban & Klopper 1973), it is still uncertain if a fall in plasma progesterone concentration in the last few weeks of pregnancy occurs in women as it does in other animals (Thorburn & Challis 1979). If primigravid patients are rigidly selected, a fall in the plasma concentration of progesterone and rise in the plasma concentration of oestrogens before parturition can be demonstrated (Csapo *et al.* 1971; Turnbull *et al.* 1974). However, studies of more representative patients showed that labour can be initiated without a fall in progesterone or rise in oestrogen (Turnbull *et al.* 1977; Mathur *et al.* 1980; Hartikainen-Sorri *et al.* 1981). The role of cortisol in the initiation of human labour remains unclear also. Maternal and fetal glucocorticoids exchange rapidly in both directions (Murphy *et al.* 1974; Fencl *et al.* 1976) but glucocorticoid secretion by the human fetus does not appear to rise before the onset of labour (Ohrlander *et al.* 1976). During the course of labour, cortisol rises in both fetal and maternal plasma (Ohrlander *et al.* 1976).

Most of the steroid hormones circulate bound to proteins. It has been suggested recently that bound steroid is taken up by target cells (Pardridge 1981; Siiteri *et al.* 1982). However, it is generally considered that the physiologically active forms of steroid hormones, capable of interacting with intracellular steroid receptors, are the small fractions of them which circulate free or unbound to macromolecules. In this study we examined whether 'progesterone withdrawal' occurs in women before the onset of labour by a decrease in the free, physiologically active fraction of the hormone in peripheral plasma. Total and free concentrations of cortisol were measured to assess relative binding of cortisol and progesterone to plasma proteins, as transcortin and albumin bind both hormones (Westphal 1971). In addition, the availability of oestradiol-17β to the uterus at this time was measured in terms of its total and free concentration in plasma.

Subjects and methods

Chemicals

All chemicals were analytical grade and solvents were redistilled before use. Peroxides and other oxidizing agents were removed from diethyl ether (Vogel 1948) before distillation. Amersham International (Sydney, Australia) supplied [1,2,6,7-^{3}H]-progesterone (87 Ci/mmol), [1,2,6,7-^{3}H]-cortisol (85 Ci/mmol), [2,4,6,7-^{3}H]-oestradiol-17β (95 Ci/mmol) and a radioimmunoassay kit (IM.1041) for the determination of total oestriol in human plasma. The radioactive steroids were routinely repurified by thin-layer chromatography on silica gel using solvent systems recommended by the supplier.

Subjects and blood sampling

Twenty-six pregnant women, ranging in age from 21 to 42 and in parity from 0 to 3, were selected on the basis of a normal, low-risk pregnancy with no history of prematurity. Subsequently, two women underwent elective caesarean section at term for cephalopelvic disproportion, and were excluded from analysis. The informed consent of each woman according to the University of Western Australia Committee for Human Rights was obtained before the study. One to three blood samples (10 ml, heparinized) were taken from the antecubital vein between 38 and 40 weeks gestation. Further samples were obtained at the earlier phase of rhythmic contractions (start of day 0), mid-stage 1 of labour (4–6 h), late stage 1 of labour (9 5–13·5 h), just after delivery, and 2–4 days postpartum. The blood was centrifuged to yield the plasma fraction and stored in aliquots at −20° C.

Plasma analysis

Albumin and total protein concentrations were determined by bromocresol green and biuret assays, respectively, using a Cobas Bio Autoanalyzer The between-assay coefficients of variation for albumin and total protein measured in this way were 1% and 2%, respectively.

Progesterone, oestradiol-17β and cortisol were measured by specific radioimmunoassays. Antiserum to cortisol was a gift from Dr R. J. Fairclough and antiserum to progesterone and oestradiol-17β were raised in rabbits against 4-pregnen-3,20-dione: 3-CMO·BSA and 1,3,5,(10)-estratrien-3,17β-dione-6-one:6-CMO:BSA, respectively. Steroids showing more than 1% cross-reactivity were pregnenolone (10%) and 5α-pregnanedione (45%) for the progesterone antiserum (42-B5) and corticosterone (30%) for the cortisol antiserum. None of the 21 steroids tested with the oestradiol-17β antiserum (44-B5) showed greater than 1% cross-reactivity. The assay procedures were similar to those described by Thorneycroft & Stone (1972). Progesterone was extracted from plasma before assay with 75% efficiency using petroleum ether. Oestradiol-17β and cortisol were extracted from plasma before assay with efficiencies of 85% and 75%, respectively, using diethyl ether. Isolation of the steroids by chromatography indicated that purification of the organic extracts of plasma before assay was unnecessary. Regression analysis of the values obtained for samples assayed directly or after thin-layer chromatography on silica gel gave correlation coefficients of $\geqslant$0 94. Solvent blanks were equivalent to $\leqslant$15 fmol/tube and the limits of the sensitivity of the assays (per tube) were 80 fmol for progesterone and cortisol, and 30 fmol for oestradiol-17β. This corresponded to detection limits in plasma of 0·6 nmol/l for progesterone, 0·5 nmol/l for cortisol and 0·3 nmol/l for oestradiol-17β. The intra- and inter-assay coefficients of variation of the three steroids assays were all $\leqslant 7\%$ and $\leqslant 14\%$, respectively. Total unconjugated oestriol in plasma was measured in one assay using a kit which incorporated enzymatic hydrolysis of the conjugated steroid. Oestriol concentrations determined simultaneously in standard plasmas were within 98–102% of expected values.

The free fractions of progesterone, oestradiol-17β, and cortisol were measured in duplicate by rate dialysis. Briefly, a dialysis cell of two identical compartments of volume V, separated by a semipermeable membrane of area A, was filled with the same sample of undiluted plasma. Tracer hormone was added to one compartment initially so that after dialysis for time t, the isotope distribution H was $(h_1 - h_2)/(h_1 + h_2)$ where h_1 and h_2 were the radioactivities of hormone in compartments 1 and 2.

The free hormone fraction f was calculated from:

$$-\ln (h_1 - h_2)/(h_1 + h_2) = 2ADft/V$$

where D was the membrane diffusion coefficient. In practice the 'cell permeability constant' $2AD/V$ was determined for a particular type of membrane and size of cell from preliminary experiments using hormone solutions of known free fraction. Thereafter, the isotope distribution in plasma samples of unknown steroid-free fraction were determined after dialysis for known times. The method has been validated for human female plasma and yields values comparable to those obtained by centrifugal ultrafiltration (Willcox *et al.* 1983). The intra- and inter-assay coefficients of variation were 2·6–8·1% for cortisol and progesterone, and were 10·2% and 8·8%, respectively, for oestradiol-17β. The free concentration of each steroid was obtained directly by multiplication of the free fraction and the total plasma concentration, determined separately by radioimmunoassay.

Results

All the women included in the analysis were delivered vaginally and initiated labour either spontaneously (n=11) or after their membranes had been artificially ruptured (n=13). Some of the latter group (n=8) were given oxytocin during labour. At least three plasma samples were obtained from each woman over the 24–36 h peripartum period, but the frequency and number of prepartum and postpartum samples varied from one to four. Mean plasma concentrations of protein and albumin in both groups were 62·9 (SEM 0·6, range 57·2–70·1) g/l and 35·2 (SEM 0·4, range 27·3–42·1) g/l, respectively. As these values were within the normal range for pregnant women near term (Hytten & Leitch 1971), no plasma samples were excluded from analysis.

At the onset of labour (day 0), there were no significant differences (Student's t-test) in any of the plasma hormone concentrations between those women who initiated labour spontaneously and those women whose labour was induced (Figs 1 and 2). The mean (SEM) plasma concentrations of progesterone decreased gradually in all women from 711·8 (146·9) nmol/l (spontaneous group) and 681·0 (69·7) nmol/l (induced group) at 10–17 days before delivery to 557·3 (70·3) nmol/l and 590·0 (76·7) nmol/l, respectively, at the beginning of labour. It then fell rapidly as labour progressed and was 119.9 (22·9) nmol/l and 136·8 (16·5) nmol/l, respectively, as the placenta was delivered (Fig. 1*a*). Over this period, free progesterone remained at 2–3% of its total concentration so that the free concentration of progesterone in the plasma of both groups of women matched closely the decline in its total concentration (Fig. 1*b*).

Total and free cortisol in plasma varied between 680 and 925 nmol/l and between 4·5 and 5·5%, respectively, up to term. Total circulating cortisol increased to 1243·7 (83·3) nmol/l ($P<0{\cdot}02$, spontaneous group) and 1247·5 (97·4) nmol/l ($P<0{\cdot}001$, induced group) by the end of the first stage of labour, that is 9·5 to 13·5 h after the start of rhythmic contractions in individual women (Fig. 1*c*). Concomitantly, free cortisol increased to 7·7 (0·5)% in both groups of women so that the free cortisol concentration increased approximately 2·5-fold to 98·0 (11·2) nmol/l ($P<0{\cdot}001$, spontaneous group) and 90·6 (16·0) nmol/l ($P<0{\cdot}005$, induced group), respectively (Fig. 1*d*). Total oestradiol-17β concentrations varied between 103 and 140 nmol/l before delivery in both groups, declined rapidly during labour, and were 19·2 (3·4) nmol/l (spontaneous group) and 29·6 (5·1) nmol/l (induced group) immediately after delivery. By 3 days postpartum plasma oestradiol-17β had stabilized at a basal concentration of around 3·7 nmol/l in all women (Fig. 2*a*). Free oestradiol-17β remained constant at 1·0–1·8% of its total concentration over the entire perinatal period so that the plasma profile of free oestradiol-17β reflected at a lower level its total concentration (Fig. 2*b*). The meaned plasma concentrations of free oestradiol-17β in the women ininitiating labour spontaneously were not significantly lower ($P>0{\cdot}05$) than in those women whose labour was induced (Fig. 2*b*).

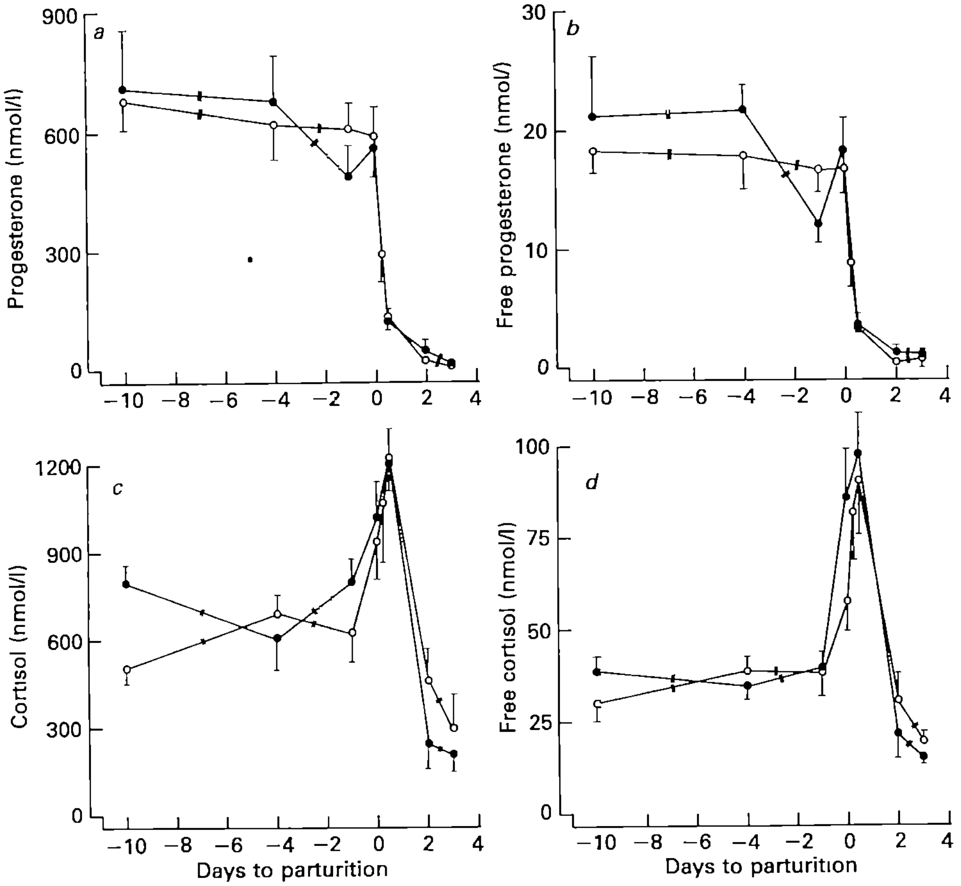

Fig. 1 The total and free concentrations of progesterone and cortisol in maternal plasma during late pregnancy and labour. (*a*) Total progesterone; (*b*) free progesterone; (*c*) total cortisol; and (*d*) free cortisol ● Spontaneous labour; ○ induced labour.

Oestriol was present in the plasma of all women in about six-fold greater amounts than oestradiol-17β. Its plasma concentration in both groups ranged between 660 and 815 nmol/l before delivery. It declined rapidly during labour and then more slowly after birth. By 3 days postpartum oestriol was present in maternal plasma at a concentration of about 20 nmol/l (Fig. 2*c*).

Discussion

We chose to measure the free steroid fraction by a rate dialysis method because it enabled analysis to be carried out at 37°C using undiluted plasma, was suitable for oestradiol-17β and cortisol as well as progesterone, and required only 0.35 ml of sample (Willcox *et al.* 1983). Free oestradiol-17β and cortisol concentrations in plasma have not been reported previously in women during late pregnancy and labour. The free progesterone fraction has been measured on three previous occasions, with conflicting results due principally to the different methods used to distinguish protein-bound hormone from free hormone. Yannone *et al.* (1969) found that 9% of plasma progesterone was unbound in eight samples obtained from two women at 39 weeks gestation and during labour. In contrast, Batra *et al* (1976) found that free progesterone increased steadily from 6% at 24 weeks of pregnancy to 13% at 40 weeks and was 19% by 2 h postpartum; in individual women, percent free progesterone doubled after delivery. In the third study, Greenstein *et al* (1977) found that 3% of the progesterone was free in the plasma of a woman sampled 23 days before delivery and subsequently 5–13 days postpartum.

This study has confirmed that the total con-

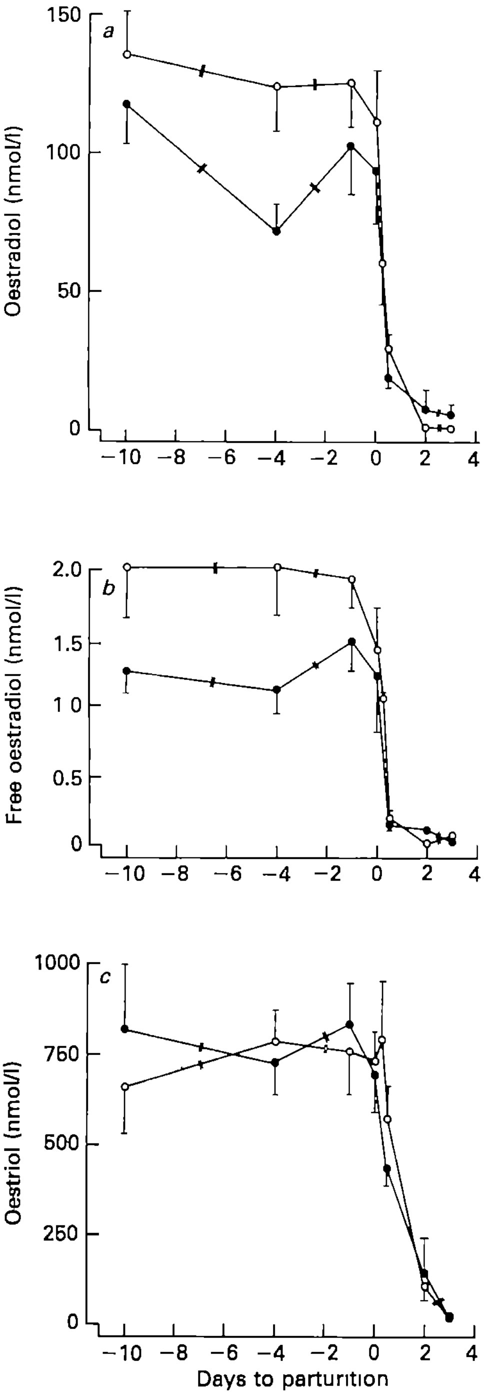

Fig. 2 Total and free concentrations of oestrogens in maternal plasma during late pregnancy and labour. (*a*) Total oestradiol-17β, (*b*) free oestradiol-17β; and (*c*) total oestriol. ● Spontaneous labour, ○ induced labour.

centrations of circulating progesterone and oestradiol-17β do not change significantly from 10–17 days pre-term to delivery in individual women whose labour starts spontaneously or is induced. Furthermore, we have shown that a redistribution of circulating progesterone in favour of the inactive bound fraction does not occur immediately before or during labour. It is unlikely that 17α-hydroxyprogesterone synthesis increased relative to progesterone synthesis at this time, since total concentrations of 17α-hydroxyprogesterone do not increase during late pregnancy and labour (Mathur *et al.* 1980). Concomitantly, the active or free fraction of circulating oestradiol does not rise. Thus in peripheral plasma there is neither 'progesterone withdrawal' nor 'oestrogen augmentation' according to Csapo's proposal (Csapo 1961; Csapo *et al.* 1971) at the onset of either spontaneous or induced labour in women.

When the hormone concentrations for individual women were normalized with respect to their initial value (obtained between 38 and 40 weeks gestation) and converted to logarithms, the mean profiles of the induced group were superimposable on those of the spontaneous group, indicating that the steroid endocrine changes with time were similar during induced and spontaneous labour. However, the data for each group have been analysed and presented separately as it might have been expected that the magnitude of the hormonal changes and the endocrine mechanisms of parturition would be different if labour was induced rather than allowed to start spontaneously.

The variety of means by which human parturition can be induced or delayed and the natural variability in the length of human gestation suggest that the initiation of labour in women involves a complex interaction of maternal and fetal neuroendocrine systems. The role of progesterone and oestrogens in this process remains unclear despite intensive investigation. It is evident from this and a number of previous studies that peripheral plasma concentrations of progesterone and oestradiol rise progressively during normal pregnancy to term and that women can go into labour without changes in the total circulating levels of these steroid hormones. This is in contrast to most animal species where plasma progesterone declines before or during parturition and oestrogen either remains high or increases during labour. In ungulates the rise in cortisol in the umbilical artery, and changes in progesterone and oestradiol in uterine venous plasma are detectable in maternal peripheral plasma (Thorburn & Challis 1979). The human fetal adrenal does not produce large amounts of glucocorticoids at term but is limited to oestrogen synthesis. It is thought that the fetal adrenal determines fetal lung maturation directly via the production of cortisol and cortisone (Gennser *et al.* 1977) and influences the timing of parturition only indirectly by providing the precursors for placental oestrogen synthesis.

The lack of consistent changes in maternal peripheral circulating concentrations of progesterone and oestradiol-17β before labour make it unlikely that these steroid hormones participate directly in the initiation of human labour. However, peripheral venous concentrations do not necessarily reflect changes in uterine venous concentrations or target organ responsiveness. Thus, progesterone and oestradiol-17β may exert their effects locally at the level of the myometrium or other intrauterine tissues (Haukkamaa & Wichmann 1977), possibly through interaction with intracellular receptors. The latter may, in turn, affect prostaglandin metabolism, either directly or via post-transcriptional events. Alternatively, these steroids may alter their biological activity by conjugation (Flint 1979). For example, oestrone sulphate rises rapidly in plasma and amniotic fluid over the last trimester (Turnbull *et al.* 1977).

The active free concentration of cortisol rose significantly ($P<0\ 005$) by the end of the first stage of labour in both groups of women. In contrast to our findings and those of others (Ohrlander *et al.* 1976; Carr *et al.* 1981), it has been suggested that total plasma concentrations of cortisol are higher after the spontaneous onset of labour than after induced labour (Murphy 1973). However, estimation of the fetal contribution to maternal circulating cortisol from measurements of the hormone in cord blood does not accurately reflect pre-labour fetal production rates (Thorburn & Challis 1979) so that the rise in fetal cortisol during labour is mainly due to maternal stress (Fencl *et al.* 1976; Gennser *et al.* 1977). The total and free concentrations of cortisol are higher in pregnancy than with non-pregnant state (O'Connell & Welsh 1969) and total cortisol rises throughout pregnancy, associated with a three- to four-fold increase in levels of transcortin (Doe *et al.* 1964). In the women monitored here total plasma cortisol began to rise as contractions began (Fig. 3*a*) so it is possible that some of the progesterone bound to transcortin was displaced by cortisol during labour. Such an effect would be minor since at this time transcortin's affinity for cortisol is less than its affinity for progesterone (Rosenthal *et al.* 1969) and the plasma concentration of progesterone was declining (Fig. 1*a*).

In conclusion, the relative amounts of free and bound progesterone in maternal plasma do not redistribute in favour of the physiologically inactive, bound form in women before labour, but our results do not preclude the possibility that 'progesterone withdrawal' occurs by altered availability to, or binding by, intrauterine tissues. Concomitantly, the amounts of total and free oestradiol-17β in plasma do not change until labour is established, when they decline. Thus the uterus is not subjected to a relative increase in circulating free oestradiol-17β as labour begins. Total and free concentrations of cortisol are elevated in maternal plasma during labour, which may be due to maternal stress but also may be an integral component of the birth process. The rises in total and free cortisol are independent of transcortin-binding effects since they occur late in labour, by which time progesterone and oestradiol concentrations are low.

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Placental protein and hormone measurements in twin pregnancy

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Summary. Maternal serum levels of human placental lactogen (hPL), schwangerschaftsprotein 1 (SP1), pregnancy-associated plasma protein A (PAPP-A), placental protein 5 (PP5) and total oestriol (E3) were measured serially in 35 twin pregnancies during the third trimester. Eighteen pregnancies had major complications including dysmaturity of one or both fetuses in nine, premature labour in six, and placental abruption in three. Serum levels of all five variables were higher than in singletons, this distinction being greatest for hPL and lowest for SP1 and E3. The levels of hPL, PP5 and E3 just before delivery were significantly correlated with the total birthweight, a correlation with placental weight being evident only for hPL and PP5. A significant correlation between the five biochemical variables at 33–34 weeks was only seen between hPL and PAPP-A. Protein and hormone levels in the abnormal twin pregnancies were not apparently different from those in the normal twin pregnancies. These data suggest that only hPL levels biochemically reflect this extreme of fetal and placental growth, but that neither the levels of hPL nor any of the other biochemical indices examined are altered in abnormalities in twin pregnancy.

Protein and steroid molecules produced by the fetus and placenta which are secreted into the maternal circulation are frequently used in the assessment of fetal wellbeing (for review see Chard & Klopper 1982). In multiple pregnancy, maternal levels of these materials, which include human placental lactogen (hPL), pregnancy-specific beta 1 glycoprotein (or schwangerschaftsprotein 1, SP1), pregnancy-associated plasma protein A (PAPP-A), placental protein 5 (PP5) and total oestriol (E3) are generally higher than in singleton pregnancies (Jandial *et al.* 1979; Gehard & Runnbaum 1980; Nisbet *et al.* 1981; Obiekwe & Chard 1981; Briet & Hoorn 1982; Westergaard & Teisner 1982). These investigations have not extensively examined maternal levels of fetoplacental products in relation to total birthweight or placental mass. Furthermore, there is no consensus on the value of estimation of these substances in the prediction of fetal compromise.

We and others (for review see Grudzinskas *et al.* 1982) have previously reported an association, albeit a tenuous one, between maternal levels of pregnancy-associated proteins and hormones in normal singleton pregnancy. As this association is considerably greater in pregnancies complicated by intrauterine growth retardation (IUGR) (Chard & Klopper 1982), it seemed logical to examine this relation in the other extreme, namely twin pregnancy. In this study we have investigated maternal levels of hPL, SP1, PAPP-A, PP5 and E3 in relation to each other, to total birthweight and placental mass, and to pregnancy outcome in 35 twin pregnancies.

Subjects and methods

A total of 153 venous blood samples were obtained at 1- to 3-week intervals from 35 consecutive women who had a clinically normal twin pregnancy when recruited at 28 weeks gestation. Serum was separated within 2 h of collection, divided into aliquots and stored at −70°C.

Estimations of hPL, SP1 and PAPP-A were performed by rocket immunoelectrophoresis and PP5 by radioimmunoassay, and compared with the 80% confidence limits of the normal range derived as described in detail elsewhere (Norgaard-Pedersen & Gaede 1973; Obiekwe *et al.* 1979; Folkersen *et al.* 1981; Westergaard *et al.* 1984). Total oestriol estimations were performed by a commercial radioimmunoassay kit (Radiochemical Centre, Amersham, UK), and the 80% confidence limits of the normal range based on 1210 samples from 627 women with normal singleton pregnancies.

The infants were assessed by an experienced paediatrician, the maturity being determined according to the Dubowitz score (Dubowitz *et al.* 1970) and dysmaturity diagnosed by birthweight (5th centile for gestational age in singletons), phenotypic characteristics and the immediate postnatal course. Placental weight was obtained after removal of blood clots, membranes and the umbilical cord.

All data were computer-stored and the statistical analyses performed according to the Statistical Package for Social Sciences (Nie *et al.* 1975). Correlation coefficients between the biochemical indices and fetal and placental weight were calculated using the blood sample obtained 1 to 11 days before delivery.

Table 1. Outcome and complications in 35 twin pregnancies

	n	Samples
Normal outcome	17	67
One twin dysmature	7	35
Both twins dysmature	2	12
Spontaneous premature labour	6	28
Placental abruption*	2	7
Stillbirth—placental abruption at term	1	4
Total	35	153

* Premature delivery, 1 patient.

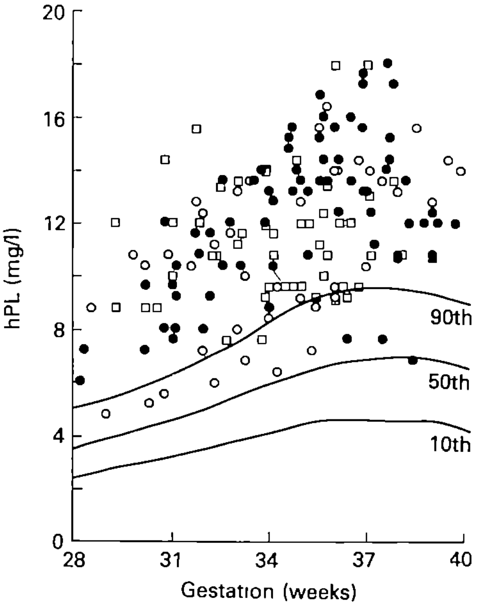

Fig. 1. Serum levels of hPL in 35 women with twin pregnancy (153 samples) in relation to the 80% confidence limits of the normal range for singleton pregnancy in the third trimester. 10th, 50th and 90th centiles for each gestational week are represented by the thick lines; ● Normal outcome at term; ○ one or both infants considered to be growth-retarded; ☐ premature delivery or placental abruption.

Results

The clinical course and outcome of the 35 twin pregnancies studied are summarized in Table 1. Serum hPL, SP1, PAPP-A, PP5 and E3 levels in relation to the 80% confidence limits of the normal range for singleton pregnancies are shown in Figs 1–5. Serum levels in twin pregnancy were generally higher than those seen in singletons for all biochemical indices examined, this difference being most pronounced for hPL (15 samples from five patients had levels less than the 90th centile) and least for total E3 (91 samples from 19 patients had levels below the 90th centile). The correlations between the biochemical indices and birthweight, and placental weight are shown in Table 2.

Significant correlations were found between hPL and E3 levels and birthweight, and between

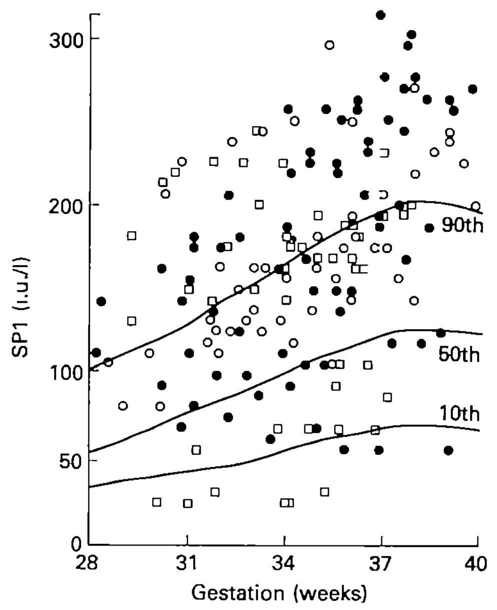

Fig. 2. Serum levels of SP1 in 35 women with twin pregnancy (153 samples) in relation to the 80% confidence limits of the normal range for singleton pregnancy in the third trimester. Symbols as in Fig. 1.

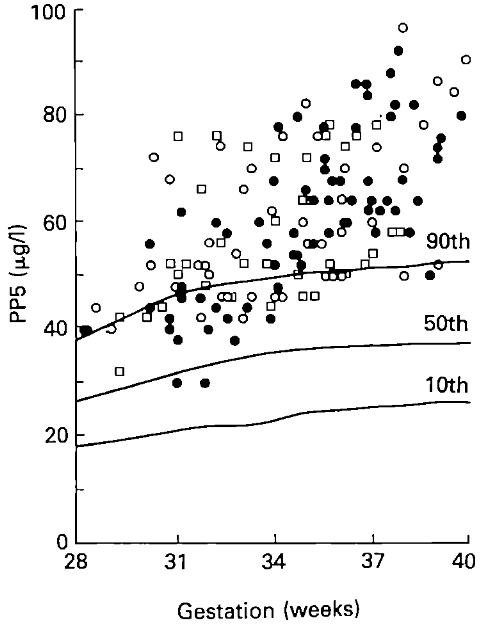

Fig. 4. Serum levels of PP5 in 35 women with twin pregnancy (153 samples) in relation to the 80% confidence limits of the normal range for singleton pregnancy in the third trimester. Symbols as in Fig. 1.

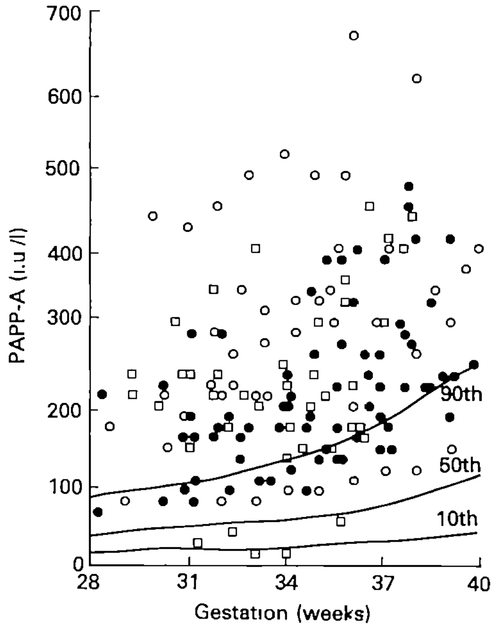

Fig. 3. Serum levels of PAPP-A in 35 women with twin pregnancy (153 samples) in relation to the 80% confidence limits of the normal range for singleton pregnancy in the third trimester. Symbols as in Fig. 1.

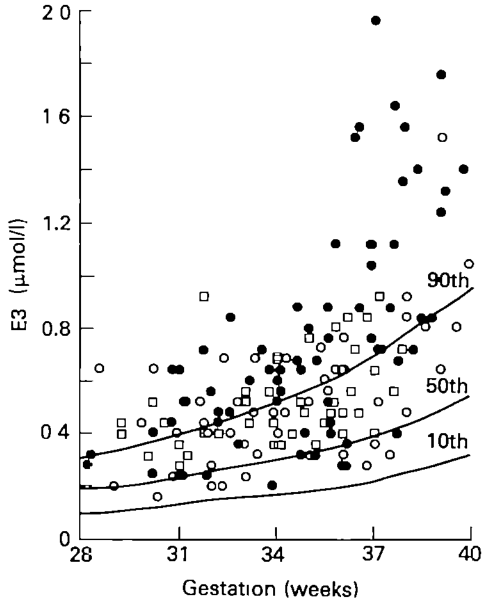

Fig. 5. Serum levels of total oestriol in 35 women with twin pregnancy (153 samples) in relation to the 80% confidence limits of the normal range for singleton pregnancy in the third trimester. Symbols as in Fig. 1.

Table 2. Correlation (Spearman's rank correlation coefficient) between serum levels of hPL, SP1, PAPP-A, PP5 and E3 and total birthweight and placental weight in 35 twin pregnancies

	hPL	SP1	PAPP-A	PP5	E3
Birthweight	0·51***	−0·07	−0·03	0·37*	0·40**
Placental weight	0·53***	−0·06	−0·13	0·34*	−0·21

* $P<0·5$; ** $P<0·01$; *** $P<0·001$.

Table 3. Spearman's rank correlation coefficient analysis between hPL, SP1, PAPP-A, PP5 and E3 at weeks 33–34 in 35 twin pregnancies

	hPL	SP1	PAPP-A	PP5
Total E3	0·14	−0·06	0·09	0·12
PP5	0·17	−0·08	−0·04	—
PAPP-A	0·31*	0·19	—	—
SP1	−0·10	—	—	—

* $P<0·05$.

maternal hPL and placental weight. Less pronounced but nevertheless significant correlations were seen between PP5 levels and birthweight, and placental weight. SP1 and PAPP-A levels did not appear to be related to birthweight or placental weight. The correlation analysis between levels of the five fetoplacental products in samples obtained at weeks 33–34 is shown in Table 3, a small but statistically significant relation being seen between hPL and PAPP-A only. Maternal levels of placental proteins and hormones did not appear to be related to the specific complications of pregnancy encountered in this group (Figs 1–5).

The rank order of serum levels of the various products in individuals was maintained throughout the period of pregnancy studied. Neither rises nor falls in the trends of levels were seen before any clinical event.

Discussion

The extreme but normal biological manifestation of fetal and placental growth seen in multiple pregnancy has presented a unique opportunity to examine the physiology and clinical consequence of proteins and hormones synthesized at these sites. In this study we have confirmed earlier reports and have expanded the information available on these substances in this condition. Although the great distinction between hPL levels in singleton and twin pregnancy was not a surprising finding, it is curious that for a fetoplacental product such as oestriol, this difference was less conspicuous. Furthermore, the difference in SP1 levels was also poor, an unexpected observation given that the association between SP1 levels and birthweight in singletons is almost equivalent to that of hPL (Gordon *et al.* 1977). Conversely, the high levels of PAPP-A and PP5 in twin pregnancy could not have been predicted from earlier observations in normal and abnormal singletons where the relation with birthweight is relatively poor (Obiekwe *et al.* 1980; Westergaard *et al.* 1982).

These data suggest that the factors which control the synthesis of these substances are largely independent of those which influence fetal growth. Detailed statistical analysis of these data support this contention, the sole exception being hPL. Nevertheless, statistically significant correlations were also observed between PP5 and E3 levels just before delivery, and birthweight, and PP5 and placental weight. Although a small but significant correlation was observed between hPL and PAPP-A, the absence of any apparent association between the other biochemical indices examined here further supports the notion that their metabolism is independent and coincidentally rather than biologically related to fetal growth factors. Finally our data on pregnancies with abnormal outcome offer no evidence that measurement of any of these biochemical indices, in contrast to singletons, might be of any value in the management of twin pregnancy.

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Does ultrasound examination render biochemical tests obsolete in the prediction of early pregnancy failure?

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Summary. Serum levels of fetal, placental and maternal hormones and proteins [α-fetoprotein (AFP), human chorionic gonadotrophin, human placental lactogen, schwangerschaftsprotein 1, pregnancy associated plasma protein-A (PAPP-A), oestradiol-17β, progesterone, pregnancy zone protein] were measured in 108 women with bleeding during the first half of pregnancy. Ultrasound examination at the time of each blood sampling revealed a fetal heart action on at least one occasion in 77 women. Spontaneous abortion occurred in 42 pregnancies, 31 of these showed no ultrasound sign of fetal life, whilst the fetal heart action was observed repeatedly until abortion in the remaining 11 women. Abnormally low levels of PAPP-A were most likely to indicate pregnancy failure, in particular if the fetal heart action was seen at the time of blood sampling. The predictive value, sensitivity and relative risk of a single depressed PAPP-A level were respectively 49, 89 and 41%, the predictive value of a normal result being 99%. With the exception of AFP, all other biochemical indices examined were consistently in the normal range in this group of women. If ultrasound findings were not considered, the biochemical indices were of comparable value in the prediction of spontaneous abortion. PAPP-A levels were uniformly depressed in all patients who spontaneously aborted, frequently weeks before this event, in the presence of a live fetus.

Serum levels of hormones and proteins of fetal, placental and maternal origin have been used to predict the outcome in threatened abortion (Niven *et al.* 1972; Nygren *et al.* 1973; Garoff & Seppälä 1975; Kunz & Keller 1976; Braunstein *et al.* 1978; Schultz-Larsen & Hertz 1978; Damber *et al.* 1978; Jovanovic *et al.* 1978; Joupilla *et al.* 1979; Masson *et al.* 1983*a, b*; Salem *et al.* 1984). Ultrasound scanning has revolutionized this practice, and some of these tests have been regarded as obsolete if fetal life can be demonstrated by ultrasound (Joupilla *et al.* 1980*a, b*; Hertz *et al.* 1980).

Nevertheless, a proportion of patients in whom

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fetal heart action has been demonstrated will spontaneously abort (Joupilla *et al.* 1980*a, b*). Furthermore, we have found that low levels of circulating pregnancy-associated plasma protein A (PAPP-A) in patients with threatened abortion but with a live fetus can differentiate between those pregnancies which will have a normal outcome and those which will not (Westergaard *et al.* 1983). In this study, we have assessed circulating levels of various fetal, placental and maternal proteins and hormones [α-fetoprotein (AFP), human chorionic gonadotrophin (hCG), human placental lactogen (hPL), schwangerschaftsprotein 1 (SP1), pregnancy-associated plasma protein A (PAPP-A), progesterone (P), oestradiol-17β (E_2), pregnancy zone protein (PZP)] in conjunction with simultaneous ultrasound examination, in the prediction of pregnancy outcome in patients with threatened abortion.

Subjects and methods

During a 2-year period (from 1 January, 1979) all patients admitted with an initial diagnosis of threatened abortion at between 7 and 20 weeks gestation to the Department of Obstetrics and Gynaecology, Odense University, were considered for this study. All the patients had an ultrasound scan (Vidoson 635, ST-real-time scanner, Siemens, and Model-3130 real-time scanner, Kranzbuhler and Sohn) within 48 h and any patient who aborted during this time was excluded from this analysis. Furthermore, patients in whom a provisional diagnosis of blighted ovum, missed abortion, molar pregnancy and ectopic gestation could confidently be made on clinical and ultrasound findings were also excluded. In the remaining 108 patients the history and clinical findings were indicative of threatened abortion and ultrasound revealed fetal heart action in 77 of them whereas repeated examination during the first week of study failed to provide clear-cut evidence of fetal life in the other 31 patients. Ultrasound scans were done at weekly intervals for 3 weeks and every 2 weeks thereafter, unless otherwise indicated by vaginal bleeding.

Maternal venous blood was obtained at the time of each ultrasound scan and samples obtained within 24 h of abortion were excluded from analysis. Serum was separated within 2 h of collection and stored at −20°C. Maternal serum levels of SP1, PZP and PAPP-A were measured by electroimmunoassay and radioimmunoassay as described previously (Westergaard *et al.* 1979; Folkersen *et al.* 1980, 1981; Sinosich *et al.* 1982). AFP, hCG, hPL, E_2 and progesterone were measured by radioimmunoassay (AFP: RIA-Gnost, Behringwerke, W. Germany; hCG: Beckton Dickinson, USA; hPL: Amersham, UK; progesterone: Diagnostic Products Corporation, USA; E_2: Eidg. Inst. für Reaktorforschung, Switzerland).

The 80% confidence limits up to 20 weeks gestation were determined from a large prospective study population consisting of 721 samples from 211 women (PAPP-A); 976 samples from 312 women (SP1 and PZP); 632 samples from 152 women (hCG, hPL, E_2 and progesterone) obtained between 7 and 20 weeks gestation. The 97·5th centile for serum AFP was derived from 632 samples from 152 women during the same interval. All women in this group were delivered uneventfully at term.

For each substance measured the results were divided into four groups: true-positives (TP) (i.e. indicative of imminent abortion), false-positives (FP), true-negatives (TN), and false-negatives (FN) (Table 1). Sensitivity was defined as the percentage of samples in the abortion group with a true-positive result [TP/(TP+FN)], whereas the predictive value of an abnormal result (PV pos) was the true positives as a percentage of all positive results [TP/(TP+FP)] and the predictive value of a normal result (PV neg) was the true-negatives as a percentage of all negative results [TN/(TN+FN)]. The relative risk of abortion was the ratio of the percentage of positives that were true-positives to the percentage of negatives that were false-negatives [TP/(TP+FP): FN/(FN+TN)] as described by Gordon *et al.* (1978).

Results

Spontaneous abortion occurred in 42 pregnancies, 31 of which showed no sign of fetal heart action on repeated ultrasound scans. In the remaining 11 patients, the fetal heart action was observed repeatedly until spontaneous abortion occurred. The number of abnormal levels of the various biochemical indices in relation to the ultrasound findings and pregnancy outcome is summarized in Table 1 and Figs 1 and 2. Tables 2 and 3 summarize the sensitivity, relative risk and predictive values of normal and abnormal levels of the biochemical indices measured in the

Table 1. Serum levels of fetal, maternal and placental products in 108 women with painless bleeding in relation to the normal range, ultrasound findings and pregnancy outcome

				Spontaneous abortion					
	Normal outcome (66 patients, 466 samples)			Evidence of fetal life by ultrasound (11 patients, 46 samples)			No evidence of fetal life by ultrasound (31 patients, 35 samples)		
	Patients <10th centile	First sample <10th centile	Samples <10th centile	Patients <10th centile	First sample <10th centile	Samples <10th centile	Patients <10th centile	First sample <10th centile	Samples <10th centile
hCG	5	4	42	1	0	3	26	26	30
hPL	5	5	40	4	2	8	19	22	23
SP1	7	7	49	2	1	3	28	28	32
PAPP-A	6	6	43	11	7	41	29	29	33
E_2	8	7	47	0	0	0	29	29	33
P	7	6	44	3	2	4	27	7	31
PZP	6	5	38	3	3	4	8	6	10
	Patients >97·5th centile	First sample >97·5th centile	Sample >97·5th centile	Patients >97·5th centile	First sample >97·5th centile	Sample >97·5th centile	Patients >97·5th centile	First sample >97·5th centile	Samples >97·5th centile
AFP	3	3	7	4	4	11	1	1	1

first sample and in all samples in relation to the ultrasound findings in the patients who aborted. The predictive value of an abnormal level in the blood sample obtained at presentation was highest for PAPP-A, in particular if there was ultrasound evidence of fetal life (54%) (Table 2). If all abnormal results were considered, i.e. from blood samples obtained serially, the predictive value was highest for AFP and PAPP-A (Table 3). In contrast, the differences between the various indices, both in single and serial samples, were less if the ultrasound findings were not considered. The sensitivity was highest for PAPP-A estimations, regardless of whether the first sample (64%) or all samples were considered, in patients with ultrasound evidence of a live fetus (Tables 2 and 3). The predictive values of a normal test were comparable for all variables and were >77% with the exceptions of AFP and PZP if the first sample was considered, the highest value (99%) was for PAPP-A estimations when all samples were considered and ultrasound demonstrated a live fetus.

Similarly, the relative risk of abortion was highest for depressed levels of PAPP-A, being at least three times greater than that for the other biochemical indices at clinical presentation, if the fetus was alive, and 5–10 times greater if all samples were considered, regardless of the ultrasound findings.

All the 11 patients who had evidence of a live fetus but subsequently aborted had depressed PAPP-A levels. In the 46 samples obtained in these patients, PAPP-A levels were abnormal weeks before abortion in four patients and in every sample obtained in the other seven (Fig. 1*d*). In contrast, the levels of the other substances measured generally remained within the normal range, the only exception being AFP (Figs 1 and 2).

Discussion

This study has expanded the information on depressed levels of PAPP-A in the prediction of pregnancy outcome in threatened abortion and compared these findings with those obtained from measurements of other fetal placental and maternal proteins and hormones. In addition the analysis of repeated simultaneous ultrasound scans, the diagnostic mainstay in threatened abortion in modern clinical practices, has provided

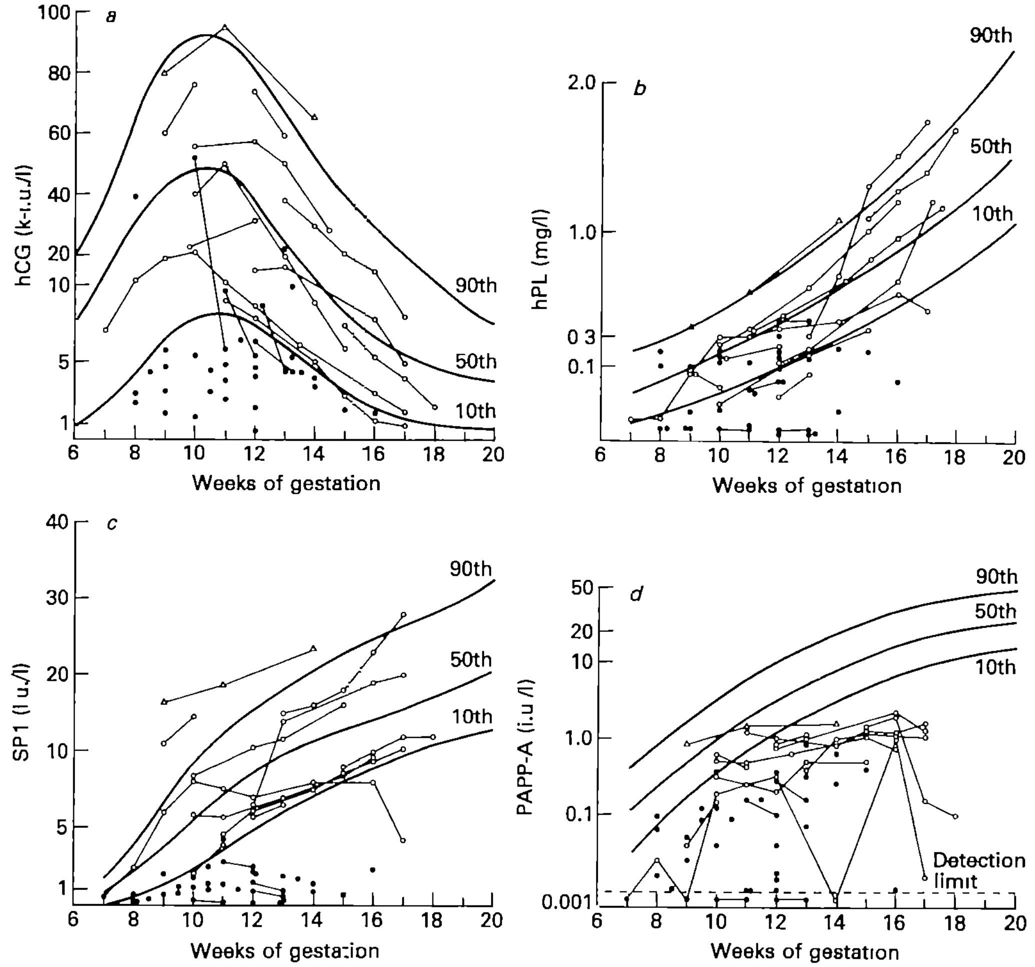

Fig. 1. Serum levels of human chorionic gonadotrophin (*a*), human placental lactogen (*b*), schwangerschaftsprotein 1 (*c*) and pregnancy-associated plasma protein-A (*d*) in 42 women with spontaneous abortion. ●, No ultrasonic evidence of fetal heart action; ○, ultrasonic evidence of fetal heart action; △, twin pregnancy with live fetuses; heavy lines represent the 10th, 50th and 90th centiles of the normal range; i.u., international units, WHO reference material for pregnancy proteins 78/610.

an opportunity to determine a rational basis for the tests used in early pregnancy complications.

The statistical predictors used have allowed us to estimate the likelihood of pregnancy failure (PV pos) if test results are abnormal, the proportion of all pregnancies which will fail and have an abnormal test result (sensitivity), as well as the relative merits of individual indicators compared with each other expressed quantitatively (relative risk factor).

In the prediction of pregnancy failure, the predictive value of an abnormal test is of primary clinical importance. In this context, an abnormal level of PAPP-A at presentation provides the most information, and AFP and PAPP-A if all sampling times are considered, the predictive values being considerably higher than any of the other indicators examined. However, as the sensitivity of abnormal PAPP-A measurements is almost four times that of AFP, the measurement of PAPP-A must be considered to have clear-cut advantages, identifying almost 90% of all pregnancies which will abort. If ultrasound results are not considered there is little to choose between the various biochemical indicators with respect to their predictive value; but as the sensitivity of a PAPP-A result is at least twice that of the other biochemical indicators, our results suggest that

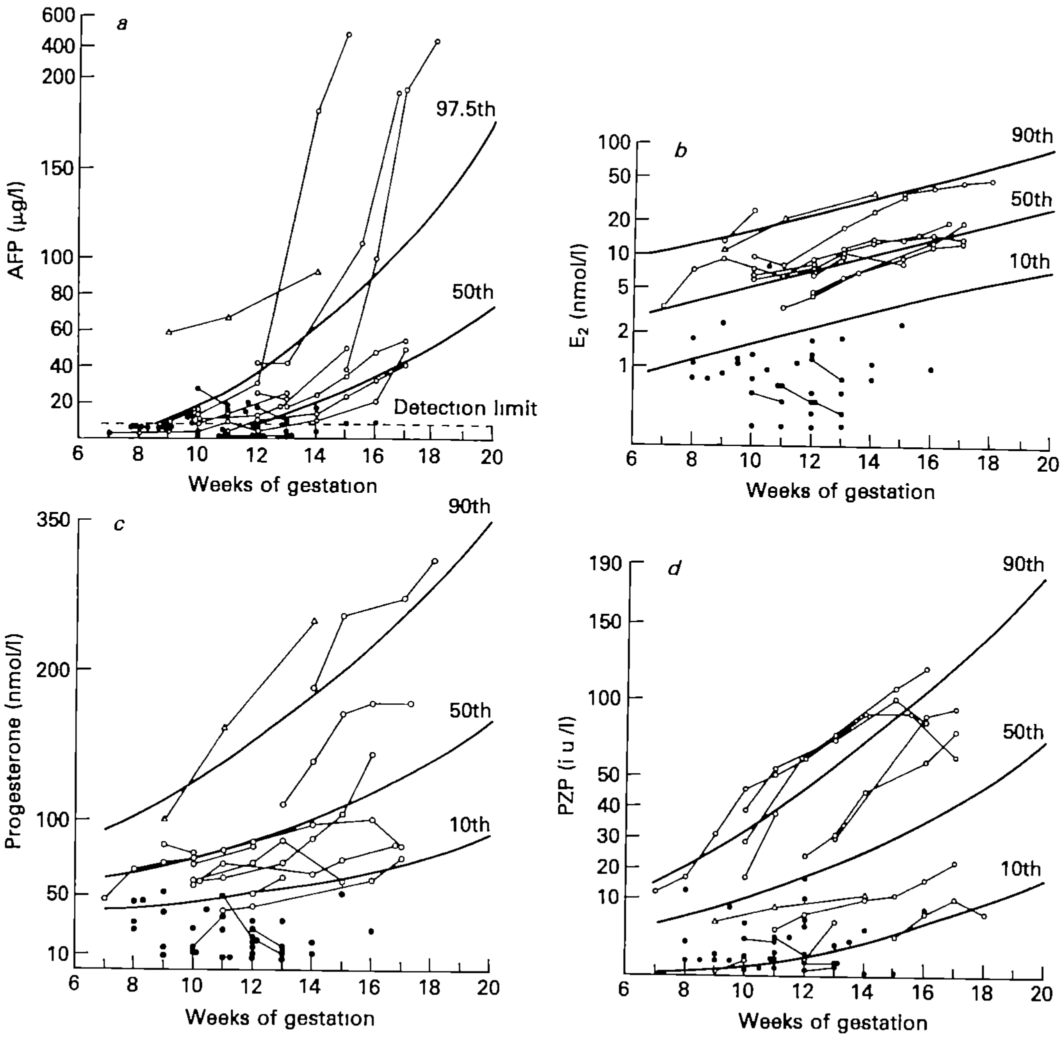

Fig. 2. Serum levels of α-fetoprotein (*a*), oestradiol (*b*), progesterone (*c*) and pregnancy zone protein (*d*) in 42 women with spontaneous abortion. ●, No ultrasonic evidence of fetal heart action; ○, ultrasonic evidence of fetal heart action; △, twin pregnancy with live fetuses; heavy lines represent the 10th, 50th, 90th and 97 5th centiles of the normal range; i.u., international units, WHO reference material for pregnancy proteins 78/610.

PAPP-A measurements provide the most useful clinical information. The relative risk of abortion was highest for PAPP-A, being at least 2–10 times greater than the relative risk calculated for the other biochemical indices.

The reliability of a normal result in predicting normal pregnancy outcome was equivalent for all indicators if ultrasound findings were not considered, although normal PAPP-A measurements were associated with a marginally greater chance of successful pregnancy. This difference was further enhanced when ultrasound was included in the analysis, 94% of all pregnancies proceeding beyond 20 weeks if the fetal heart was noted at presentation, and 99% of pregnancies proceeding beyond 20 weeks if PAPP-A levels subsequently remained in the normal range. It is noteworthy that the statistical predictions used in the analysis are not without limitations. Although the predictive value of a depressed PAPP-A level was 54% at presentation, PAPP-A levels fell in all the patients who had evidence of a live fetus but who aborted subsequently, in the majority, weeks before this event.

The present results accord with observations reported by other investigators (Niven *et al.*

Table 2. The sensitivity, relative risk and predictive values of normal (FV neg) and abnormal (PV pos) levels of fetal, maternal and placental products in single samples from patients with threatened abortion in the presence of fetal life

	hCG	hPL	SP1	PAPP-A	AFP	E_2	P	PZP
Sensitivity	0	18·2	9·1	63·6	9·1	0	18·2	27·3
	(61·9)	(57·1)	(69·0)	(85·7)	(5·0)	(67·0)	(69·0)	(21·4)
Relative risk	0	2·3	0·9	8·5	1·4	0	1·7	2·8
	(4·2)	(3·6)	(4·5)	(9·4)	(0·8)	(4·2)	(4·5)	(1·7)
PV neg	84·9	87·1	85·5	93·8	86·1	84·1	86·8	88·2
	(79·5)	(77·2)	(81·9)	(90·9)	(60·8)	(81·7)	(81·9)	(64·5)
PV pos	0	28·6	12·5	53·8	20·0	0	22·2	23·3
	(86·7)	(82·8)	(80·6)	(85·7)	(33·3)	(78·4)	(80·6)	(60·0)

Number in parentheses refer to these analyses if ultrasound results are not considered. The calculations are based on analysis of the first sample obtained at entry into the study.

Table 3. The sensitivity, relative risk and predictive values of normal (PV neg) and abnormal (PV pos) levels of fetal, maternal and placental products in single samples from patients with threatened abortion in the presence of fetal life

	hCG	hPL	SP1	PAPP-A	AFP	E_2	P	PZP
Sensitivity	6·5	17·4	6·5	89·1	23·9	0	8·7	8·7
	(40·7)	(38·3)	(43·2)	(91·4)	(14·8)	(40·7)	(43·2)	(17·3)
Relative risk	0·7	2·0	0·6	41·8	8·6	0	0·9	1·0
	(4·3)	(4·2)	(4·2)	(38·9)	(4·8)	(4·0)	(4·5)	(2·0)
PV neg	90·8	91·8	90·6	98·8	92·9	90·1	90·9	91·1
	(89·1)	(90)	(90·1)	(98·4)	(86·9)	(89·7)	(90·2)	(86·5)
PV pos	6·7	16·7	5·8	48·8	61·1	0	8·3	9·5
	(44·0)	(43·7)	(41·7)	(63·2)	(63·0)	(41·3)	(44·3)	(27·0)

Numbers in parentheses refer to these analyses if ultrasound results are not considered. The calculations are based on the analysis of all samples obtained during the study.

1972; Nygren *et al.* 1973; Garoff & Seppälä 1975; Kunz & Keller 1976; Braunstein *et al.* 1978; Schultz-Larsen & Hertz 1978; Jovanovic *et al.* 1978; Joupilla *et al.* 1979, 1980*a*, *b*; Hertz *et al.* 1980, Salem *et al.* 1984), in particular if the ultrasound findings are not considered. Minor discrepancies with earlier reports can be attributed to the heterogeneity of the various populations studied, since all the women included in the present study had classical symptoms and signs of threatened abortion only. Other differences may be due to the design of earlier studies such as scanty ultrasound data, the numbers of patients studied, and assay differences.

When considered together with the ultrasound findings, our data on circulating levels of proteins and hormones of fetal, placental and maternal origin in patients with threatened abortion show that abnormal levels may be of secondary importance in the pathophysiology of this condition. PAPP-A would appear to be the sole exception for the following reasons. First, low PAPP-A measurements are associated with imminent abortion in women who have painless bleeding and a living fetus. Second, it must be emphasized that all patients who aborted had abnormal concentrations of PAPP-A weeks before the abortion while the fetus was still alive. Serial estimations of PAPP-A can enhance the clinical value of these measurements, permitting the diagnosis of imminent pregnancy failure, in situations previously beyond the range of any diagnostic tool.

Acknowledgments

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Long-term culture of human trophoblast cells

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Summary. A technique is presented for the preparation of cultures of replicating human trophoblast cells from term placentas. The adherent cells obtained were very slow growing (doubling time 12·5 days) as measured by the rate of increase in cell protein, [^{14}C]-leucine uptake and cell number. Cells from individual placentas have been maintained in continuous culture for up to 1 year (10–12 passages) and have been successfully recultured after storage in liquid nitrogen. Cultured cells showed positive immunofluorescent staining for human placental lactogen, human chorionic gonadotrophin, transferrin and type IV collagen. The adenine nucleotide content indicated that energetically the cells were in balance even after prolonged culture.

Obstetricians tend to take the placenta for granted, except on the rare occasions when it appears to fail. However, this most readily available of human tissues fulfils nutritional, metabolic, excretory and immunological roles that are essential for fetal development. In addition the placenta differentiates and grows from an embryonic to a mature tissue and on to what many clinicians consider to be senescence in only 9 months. During this time it passes through the stages of allograft acceptance, differentiation, invasive growth, maturity and finally 'rejection'. This multiplicity of metabolic and immunological processes and control mechanisms makes the placenta of potential interest to a wide range of biomedical research workers. Differences in placentation between species means that animal studies are of limited value in the interpretation of human placental function and ethical considerations severely limit in-vivo studies in women. Hence the need to develop alternative in-vitro methods.

The isolated perfused lobule preparation (Krantz *et al.* 1971; Schneider *et al.* 1972; Penfold *et al.* 1981*a*, *b*; Drury *et al.* 1981) offers a means of examining the intact human organ. Tissue slice (Genbačev *et al.* 1982) and explant culture (for review see Stromberg 1980) have also been used. All are essentially short-term approaches since the duration of perfusion experiments and tissue-slice survival are measured in hours while rapidly growing fibroblast-like stromal cells soon predominate if explant cultures are maintained for more than 7–10 days, the more so if term placenta is the starting material. Furthermore, replicate samples cannot easily be obtained.

In principle, cell culture methods offer a reproducible experimental system able to sustain long-term studies and provide as many replicate samples as may be required. Direct comparisons between different experiments become possible and such preparations could afford a means of extending current studies of placental function to the cellular level. Attempts to establish replicating cultures of normal human placental cells have met with limited success due in part to short survival of the trophoblastic cells, overgrowth by stromal fibroblasts (for review see Stromberg 1980) or failure of the cells to replicate (Paul *et al.* 1978; Stromberg *et al.* 1978; Niazi *et al.* 1981) although cells have been maintained in static culture for 6–22 months (Paul *et al.* 1978; Cotte *et al.* 1980).

We present here a technique for the preparation of monolayer cultures of replicating human trophoblastic cells from term placentas. A preliminary account of some of this work has already been published (Morgan & Toothill 1984).

Material and methods

Materials were obtained from the following UK suppliers: medium for tissue culture, Flow Laboratories, Irvine, KA12 8NB, or Gibco-Biocult, Paisley, PA3 4EP; multiwell slides, No. 60-408-05, Flow Laboratories; radiochemicals, Amersham International, Amersham, HP7 9LL; Basol F-220, Gramos Chemicals, Portsmouth PO3 5NT; immunoglobulin (Ig) fractions of rabbit antisera to human chorionic gonadotrophin, placental lactogen and transferrin, rabbit immunoglobulin fraction and fluorescein isothiocyanate (FITC) conjugated swine antiserum to rabbit Ig from Dacopatts, Denmark, were obtained through Mercia-Brocades, Weybridge, KT14 6RA; FITC-conjugated rabbit antiserum to whole guinea-pig serum, Wellcome Reagents, London SE13 6TL; human transferrin, Sigma Chemicals, Poole BH17 7NH; guinea-pig antisera to human collagen were a gift of the Section of Dermatology in this Institute.

Preparation of primary cultures

Human placentas were obtained from normal full-term vaginal deliveries and processing of the tissue was begun within 10 min of delivery. The membranes, chorionic and decidual plates were removed and cubes of healthy-looking villous tissue were rapidly dissected out and placed in ice-cold phosphate-buffered saline (PBS ‘A’; Dulbecco & Vogt 1954) containing 100 µg/ml each of penicillin and streptomycin (PBSPS) for transport to the laboratory. Portions of tissue (20 g) were chopped finely with sterile scissors then washed twice by decantation with PBSPS. A sterile PTFE-covered stirring bar was added to the mince which was then digested with trypsin–versene (0·25% trypsin, 0 25% Na_2 EDTA in PBSPS; 100 ml/20 g tissue) at room temperature with low-speed stirring. Time from delivery of the placenta to the start of digestion was usually 1 h. After 15 min the supernatant was removed from the digest by decantation and discarded. The trypsin treatment was repeated for further periods of 15, 30, 60 and 150 min. After the final trypsinization the resulting suspension was filtered through three layers of sterile surgical gauze to remove any fragments of tissue that remained and a viscous gel that sometimes formed. Cells in the filtrate were sedimented by centrifugation at 240 *g* for 15 min then resuspended in culture medium (Ham’s F-12 medium supplemented with 30% fetal calf serum, 2 mM glutamine and 100 µg/ml each of penicillin and streptomycin; 40 ml/20 g original tissue). Portions of the cell suspension (10 ml) were dispensed into 80-cm² tissue culture flasks, the caps screwed tight as recommended by Aladjem & Lueck (1981), and the flasks incubated at 37°C in an atmosphere of 95% air–5% CO_2. After 2 weeks the medium was removed, replaced by fresh medium and the flasks were again tightly sealed. Cultures were examined at intervals using an inverted phase-contrast microscope. When clusters of proliferating cells could be seen (usually after a further 2–4 weeks) the flask caps were loosened and the cultures fed twice weekly by removing half the medium and replacing it with fresh. Cultures usually reached confluence 6–10 weeks after inoculation.

Subcultures

Medium was removed from confluent monolayers and the cell sheet washed three times with PBS ‘A’ then 5 ml of trypsin solution (0 25% trypsin, 0 25% Na_2 EDTA in PBS ‘A’) added to each 80-cm² flask. After 1 min in contact with the cells, 4 5 ml of the solution was removed and the flask incubated at 37°C. After 30 min the flask was tapped firmly to loosen adherent cells, 10 ml of fresh medium added and 5 ml portions of the resulting cell suspension transferred to new flasks containing 5 ml of fresh medium to give a split ratio of 1:2. Subcultures prepared in this way and fed twice weekly usually reached confluence in 25–30 days. Cell viability was determined by Trypan blue exclusion.

Cryopreservation and subsequent recovery of cultured cells

Cultures to be preserved were treated with trypsin as described, washed by suspension in, and centrifugation from, culture medium (5 ml/flask). The cell pellet was resuspended in 1 ml of culture medium containing 10% dimethyl sulphoxide, transferred to a 2-ml plastic screw-capped ampoule, and frozen by gradual immersion in liquid nitrogen.

Cells recovered from frozen storage were rapidly thawed by immersing the ampoule in a water bath at 37°C. After centrifugation (240 *g*) the supernatant fluid was discarded and culture medium (1 ml) added dropwise with shaking, to the cell pellet. The resuspended cells were transferred to a 25-cm^2 culture flask containing 2 ml of medium and grown up as described for subcultures.

Growth kinetics

The rate of growth of the cells in culture was examined by measuring leucine and thymidine uptake, increase in cell number and in cell protein. For these experiments cells were seeded in 25-cm^2 flasks using one-third of the quantities described above and 3 ml of medium per flask. Counts were performed on cells grown in flasks marked with a 4-mm grid. At intervals flasks were removed from the incubator, the cell sheet was rinsed three times with PBS 'A' then stained *in situ* with May–Grunwald (2 ml/flask; 2–3 min) then Giemsa's (2 ml/flask; 5 min) stains. The number of nuclei in each of eight squares (eight fields of the ×10 objective on the inverted microscope) were counted by two independent observers and the results averaged.

Leucine uptake was measured following addition of L[1–^{14}C]-leucine (54 mCi/mmol; 50 µCi/ml; 250 µl) to duplicate flasks; after 48 h the cell sheet was washed three times with PBS 'A' then digested for 1 h at 37°C with Lowry reagent C (Lane 1957). A portion of the digest (0 5 ml) was added to 3·5 ml of a Triton-toluene cocktail (Triton X-100, 600 ml; toluene, sulphur-free, 1400 ml 2,5-diphenyloxazole (PPO), 10 g; 1,4-bis[2-(5-phenyloxazolyl)]-benzene (POPOP), 100 mg) and the radioactivity determined by liquid scintillation counting.

Thymidine uptake was measured as described for leucine except that [methyl-^{3}H]-thymidine (0 2 Ci/mmol; 53 µCi/ml; 125 µl/flask) was substituted for [^{14}C]-leucine.

Cell protein was determined by the Lowry method (Lane 1957) on the remaining portions of the digests.

Immunofluorescent staining

Glass multiwell slides were washed in detergent (Basol F220), thoroughly rinsed in tap water then distilled water and heat sterilized. Cells were diluted in culture medium to a concentration of 2×10^5 cells/ml and 50 µl of cell suspension placed in each well. The slides were then incubated at 37°C for 7 days in a humidified atmosphere of 95% air/5% CO$_2$. Cultures to be stained for collagen had ascorbic acid (25 µg/ml) added to the medium.

Established cell monolayers were rinsed in HEPES-buffered RPMI 1640 (containing 2% fetal calf serum), exposed to normal Ig or serum corresponding to the first antibody (10 min), rinsed in medium, and coated with antibody diluted in HEPES-RPMI medium (30 min); after thorough rinsing in three changes of medium (10, 10, 20 min), the cell sheets were exposed to the appropriate second normal serum (5 min), rinsed in medium, and coated with FITC-labelled second antibody (30 min). The stained cells were thoroughly washed, as before, and mounted in 50% glycerol in PBS 'A' containing 1 mg/ml *P*-phenylenediamine (Johnson & Aranjo 1981).

In control experiments the first antibody was replaced by normal rabbit Ig or guinea-pig serum (serum control) or medium (conjugate control). Cultures used to demonstrate the presence of transferrin receptors were first exposed to human transferrin (20 mg/ml in HEPES-RPMI) for 30 min as described by Galbraith *et al.* (1980).

Electron microscopy

Cultured cells were fixed *in situ* by exposure overnight to 3% glutaraldehyde in 0 1 M sodium cacodylate buffer, pH 7 2; post-fixed in osmium tetroxide, dehydrated using an ascending series of alcohols and the solvent removed in a critical point apparatus. Specimens were examined in a Phillips SEM 500 scanning electron microscope.

Hormone secretion

Medium from cultures was centrifuged to remove any cell debris and the content of human chorionic gonadotrophin (hCG), human placental lactogen (hPL), progesterone and oestradiol estimated by radioimmunoassay at the MRC Human Reproduction Group, Princess Mary Maternity Hospital, Newcastle upon Tyne, UK.

Adenine nucleotide content

Following removal of the culture medium cell sheets were rinsed three times with PBS 'A' and treated with trypsin as described before. The detached cells were sedimented by centrifugation and extracted with trichloroacetic acid. The adenine nucleotide content of the extract was determined as described by Simmonds *et al.* (1982).

Results and discussion

Cell protein, leucine uptake and cell number increased with time in culture for 25–30 days then reached a plateau (Fig. 1). The slow-growing cells (doubling time 12.5 days) entered the log phase of growth about the eighth day after seeding and maintained this rate of growth for 10–12 days. Thymidine uptake could not be used as a progressive indicator of cell growth since most of the thymidine uptake occurred in the first few days of growth (Fig. 2). Similar kinetics have been reported for thymidine incorporation by placental organ cultures (Huot *et al.* 1979) and cultured human keratinocytes (Davison *et al.* 1979). Problems that can arise from the use of [^{3}H]-thymidine incorporation to measure cell proliferation have been reviewed by Maurer (1981).

Cells from 11 out of 14 individual placentas have been maintained in continuous culture for 10–12 months (10–12 passages), a success rate of about 80%, before the generation time increased and the cultures began to degenerate. Although these cells grow very slowly, their period of active multiplication compares well with that of other human diploid cells in culture. The doubling time for epithelial cells is about twice that for fibroblasts (Le Guilly *et al.* 1973) and Hayflick (1965) has shown that time in culture rather than number of passages is the determining factor in the life-time of cultured cells. Previous explanations offered for failure to establish long-term cultures of placental cells have been based on the belief that the term placenta is a senescent tissue (Vincent *et al.* 1976); the finding by Le Guilly *et al.* (1973) of a negative correlation between the life-span of a culture and the age of the donor; and reports that fibroblast-like cells derived from donors genetically disposed to premature ageing have a shortened life-span in culture (Martin *et al.* 1965; Goldstein 1969). However, Fox (1979) concluded that 'a critical review of the available data revealed little conclusive evidence of true placental ageing'. Cells prepared as described herein have been re-established in culture after storage in liquid nitrogen for 6–9 months with no effect on their total lifespan in culture.

Positive immunofluorescent staining of high passage cultures was obtained with antibodies to hCG, hPL, and type IV collagen (Fig. 3), all accepted markers of trophoblastic cells (Stromberg 1980). The presence of transferrin receptors

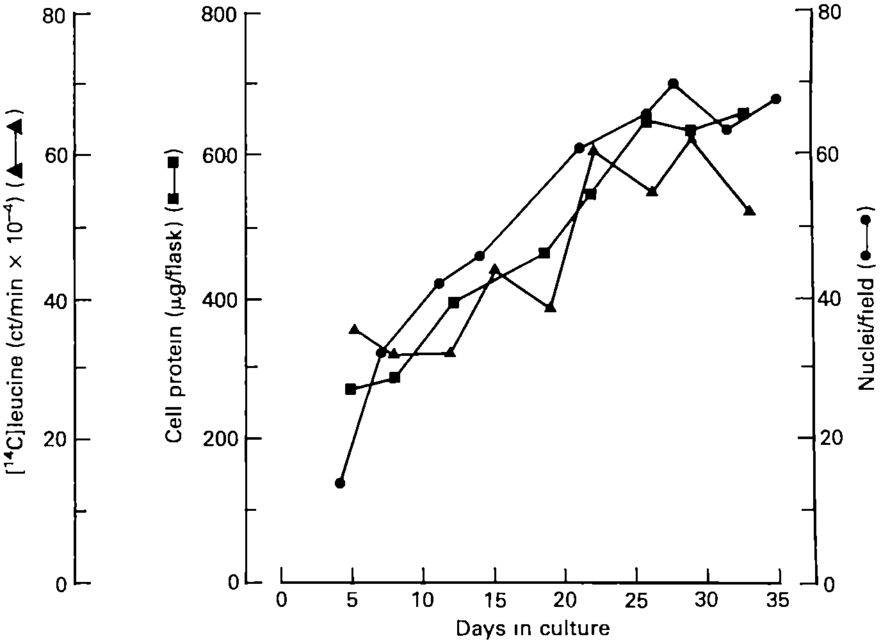

Fig. 1. Rate of growth of trophoblasts in culture as shown by increase in cell number, cell protein, and [^{14}C]-leucine uptake. Cells were used at passage six after 5 months in culture. Split ratio was 1:2.

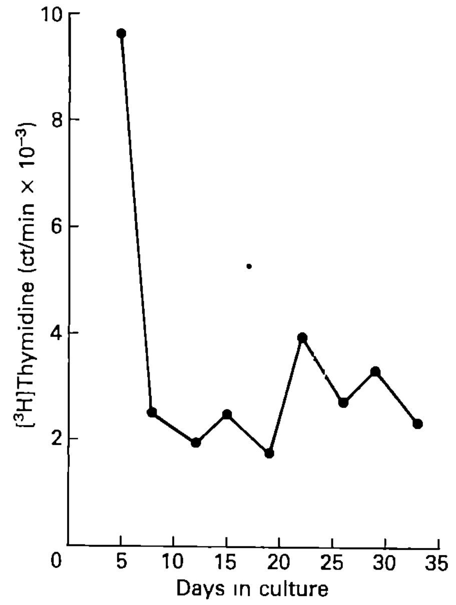

Fig. 2. Time course of thymidine uptake by cultured trophoblasts. For details see legend to Fig. 1 and text.

on the cell surface was also demonstrated. Negative results were obtained using antisera to type I and type III collagens, which are secreted by fibroblasts. Controls were negative when photographed under identical conditions.

Hormone secretion declined rapidly with time in culture (Table 1) as found by others (Hall *et al.* 1977; Stromberg *et al.* 1978; Cotte *et al.* 1980) and may result from the absence of essential precursors or other factors following removal of the cells from their normal environment. In contrast oestradiol is secreted into the culture medium at rates explicable in terms of aromatization by the cells of the testosterone present in the fetal calf serum (average 40 ng/100 ml, range 21–99 mg/100 ml; Price & Gregory 1982); a property not confined to trophoblastic cells (Callard *et al.* 1980; Rommerts *et al.* 1982).

Morphologically the cells resembled those reported by others (Fox & Khankongor 1970; Loke & Borland 1970; Stromberg *et al.* 1978; Lueck & Aladjem 1980) (Figs 4 and 5), showed signs of syncytia formation, and became multinucleate as they approached confluence (Fig. 6). In general confluent cell sheets exhibited contact inhibition but this was not always so. On occasion cells from particular placentas grew to much higher densities and piled up on each other (Fig. 7). An extreme case is shown in Fig. 8. It is unlikely that the cells had become transformed as they survived in culture no longer than contact-inhibited cells. It is tempting to speculate that this phenomenon may have some connection with the stage of invasive placental growth *in vivo*.

The adenine nucleotide content of trophoblast cells after 10 months in culture (10 passages) is shown in Table 2 together with the calculated energy charge (Atkinson 1968). The value obtained (0·85) compares well with other values for cultured cells (Lothrop & Uziel 1980), and placenta (Simmonds *et al.* 1982), and exceeds that for the oxygenated perfused lobule preparation (Illsley *et al.* 1984). An energy charge of 0·85 corresponds to the metabolic steady state in which ATP production is equal to ATP utilization (Lehninger 1975), hence by this criterion the cells are energetically in balance even after prolonged culture.

Table 1. Hormone secretion by cultured trophoblasts in early and late culture

	Human chorionic gonadotrophin (mU/ml)	Progesterone (pg/ml)	Oestradiol (pg/ml)	Human placental lactogen (nU/ml)
5 days after 1st inoculation	44 7	22300	414	>20
	44 9	21150	549	>20
Passage 2	0	200	98	0
	0	<500	150	0
Passage 7	<4	0	484	0
	<4	0	500	0
Passage 8	0	0	135	0
	0	0	118	0
Culture medium	0	0	<35	0

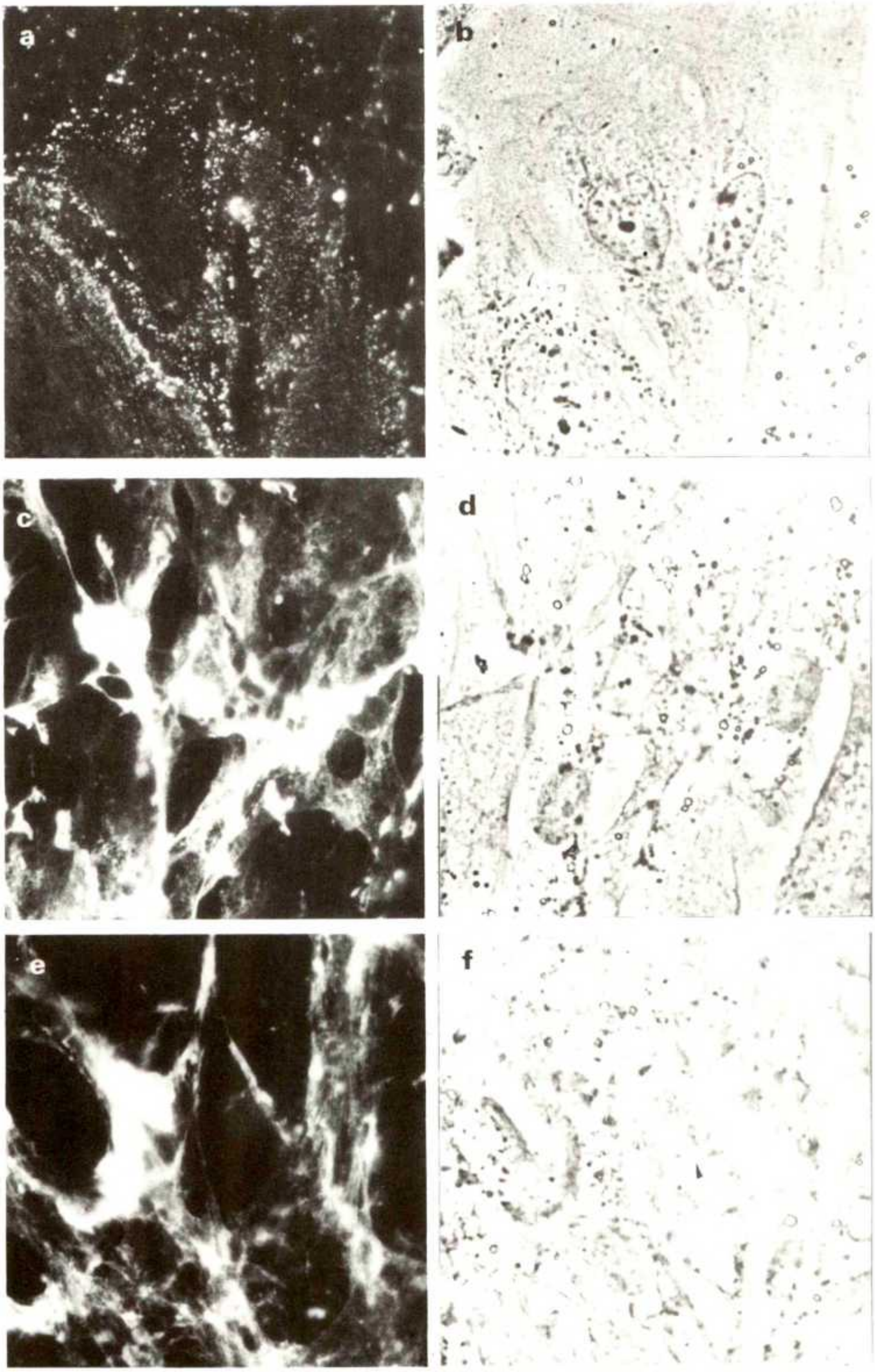

Fig. 3. Immunocytochemically stained trophoblast cultures after exposure to antibodies to: (*a*) human chorionic gonadotrophin; (*c*) human placental lactogen; and (*e*) type IV collagen. Phase-contrast photographs of the same fields (*b*, *d* and *f*) show the fluorescence to be associated with cellular structures in each case. ×500.

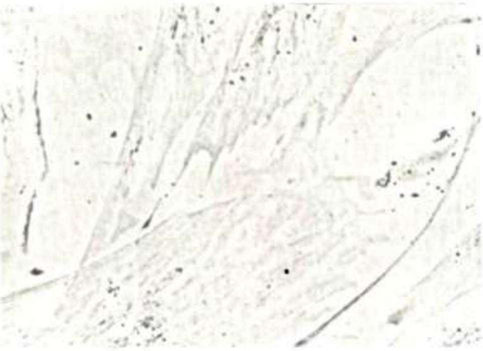

Fig. 4. Trophoblasts in culture 14 days after seeding. Phase-contrast, ×180.

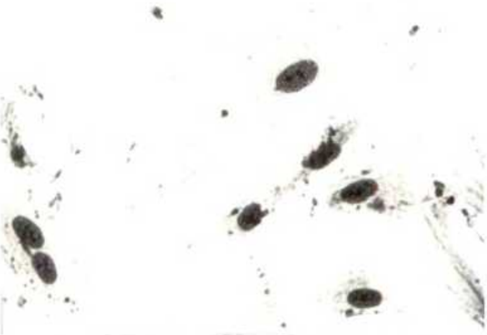

Fig. 5. Trophoblasts stained *in situ* after 10 days culture (×180). Morphologically the cells resemble those in Fig. 4, showing that this technique does not result in gross distortion of structure. Note the presence of several binucleate cells.

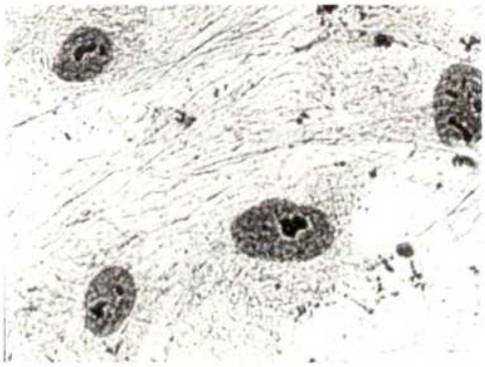

Fig. 6. Trophoblasts stained *in situ* after 30 days in culture showing apparent formation of a syncytium ×500.

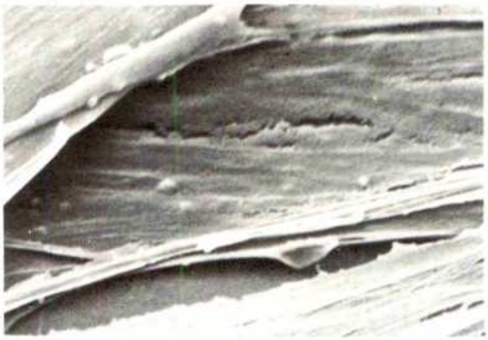

Fig. 7. Scanning electron micrograph of trophoblasts after 35 days in culture showing overgrowth of cells ×3300.

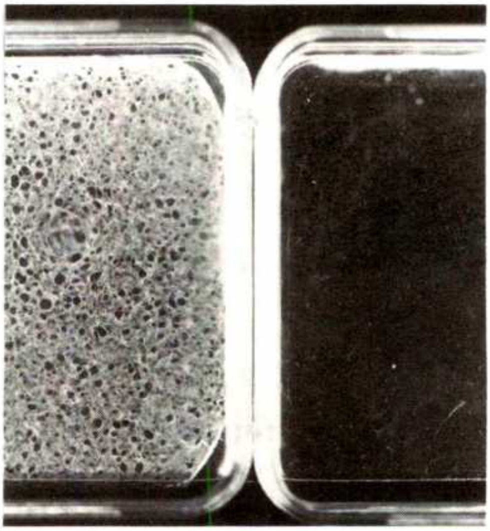

Fig. 8. Trophoblasts (left) and fibroblasts (right) after 4 months in culture, both grown under identical conditions (the flasks are 75 cm wide).

Table 2. Adenine nucleotide content and energy charge of human trophoblastic cells after 10 months in culture. Results are from duplicate assays.

Adenine nucleotide (nmol/10^6 cells)			Energy charge
ATP	ADP	AMP	
5·45	1·37	0·3	0·86
4·82	1·29	0·3	0·85

The ability to prepare cultures of replicating placental cells that can be identified morphologically and immunocytochemically as trophoblast will enable us to investigate the effects on these cells of drugs, vitamins and hormones in conditions where both dose and duration of exposure are precisely known. The ready availability of such cultures will also facilitate studies of the role of polyamine oxidase secretion in human pregnancy (Morgan *et al.* 1983) and the technique also offers a means of examining, at the cellular level, the effects of temperature, anoxia, radiation and other environmental changes on placental function.

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Amniotic fluid prostaglandins do not reflect human fetal lung maturation

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Summary. Experimental data suggest the involvement of classic prostaglandins (PG), prostacyclin (PGI_2) and thromboxane A_2 (TxA_2) in fetal pulmonary development. To explore this possibility in man, we assayed serial amniotic fluid samples from 33 women for 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (M-$PGF_{2\alpha}$, a metabolite of $PGF_{2\alpha}$), 6-keto-$PGF_{1\alpha}$ (a breakdown product of prostacyclin (PGI_2)), and thromboxane B_2 (a metabolite of TxA_2) as well as for the lecithin/sphingomyelin (L/S) ratio and phosphatidylglycerol. No difference in these prostanoids was seen between the samples with the immature (<2) or mature (≥ 2) L/S ratio, or between the samples with undetectable or detectable phosphatidylglycerol. The L/S ratio matured in 16 women and phosphatidylglycerol became detectable in 19 women during serial smpling, but even in these women the changes in the amniotic fluid prostanoids were inconsistent. It is concluded that the amniotic fluid M-$PGF_{2\alpha}$, 6-keto-$PGF_{1\alpha}$ and TxB_2 do not reflect fetal pulmonary maturity.

Functional pulmonary surfactant consists of various phospholipids, such as lecithin, sphingomyelin and phosphatidylglycerol, which are produced by pulmonary cells (Farrell & Hamosh 1978). This production can be regulated, at least in part, by glucocorticoids (Liggins & Howie 1972), cyclic AMP (Hallman 1977) and aminophylline (Gross & Rooney 1977). Because prostaglandins (PG), prostacyclin (PGI_2) and thromboxane A_2 (TxA_2) are potent biological mediators deriving from cell membrane phospholipids, particularly in pulmonary tissue (Cuthbert & Gardiner 1980), they may also be involved in fetal pulmonary maturation. This theory gains support from in-vitro and animal data (Colacicco *et al.* 1977; Powell & Solomon 1978, 1980; Oyarzya & Clements 1978; Kitterman *et al.* 1981), but no data exist on PGs, PGI_2 and TxA_2 during human fetal lung maturation. We studied the relations between the amniotic fluid concentrations of these prostanoids and biochemical indices of fetal lung maturation during human pregnancy.

Patients and methods

Thirty-three women with complicated pregnancies were studied (Table 1). Seventeen had diabetes, which was under good control with twice-daily insulin treatment. Nine women had rhesus D antibodies in their sera at a titre of 1:32 or more. Three patients had pre-eclampsia, defined as a rise in blood pressure to >140/100 mmHg. One woman had hepatogestosis, one hypothyroidism, and two intrauterine growth retardation (Table 1). No infant developed respiratory distress syndrome (RDS).

Amniocentesis was carried out under ultrasound control 2–6 times (mean 3·0 SD 1·1) with 5–7 days interval to assess fetal pulmonary maturation and/or to measure bilirubin in Rh-immunized pregnancies between 26 and 39 weeks gestation (Table 1). A part of the sample was used for the measurement of the lecithin/sphingomyelin (L/S) ratio and phosphatidylglycerol with thin-layer chromatography, as described in detail

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Table 1. Clinical characteristics of the study population

Complication	Number of women	Age (years)	Gestational age (weeks)		Birthweight (g)
			At 1st amniocentesis	At delivery	
Diabetes mellitus	17	27 1 (3 7)	36 0 (0 5)	38 0 (1 0)	3733 (651)
Rh-immunization	9	36 0 (5 5)	30·1 (3 6)	36 6 (2 5)	2998 (527)
Pre-eclampsia	3	30 3 (4 7)	34 6 (1 7)	38 0 (2 0)	2910 (1260)
Miscellaneous	4	32 2 (7 5)	36 0 (0 6)	37 1 (0 6)	2706 (300)
Total	33	30 5 (6 0)	34 2 (3 2)	37 5 (1 5)	3315 (754)

Results are means (SD).

by Hallman & Teramo (1981). The sensitivity of phosphatidylglycerol measurement was 0 5–0·8% of total acetone precipitated phospholipids. The L/S ratio was expressed as <2, 2 and >2. However, even if the L/S ratio was >2, but phosphatidylglycerol was still undetectable, the amniocentesis was repeated.

Another part of the sample was frozen immediately after the amniocentesis and used for the radioimmunoassays of 6-keto-PGF$_{1\alpha}$ (a breakdown product of PGI$_2$) and TxB$_2$ (a metabolite of TxA$_2$), as described by Ylikorkala *et al.* (1981). The mean recoveries of 6-keto-PGF$_{1\alpha}$ (50–200 pg/ml) and TxB$_2$ (25–100 pg/ml) added to the amniotic fluid were 81·1% and 77·3%, respectively. The samples from the same subjects were always assayed in the same batch, and the intra-assay variation was 7·3% for 6-keto-PGF$_{1\alpha}$ and 9 8% for TxB$_2$ (n = 15). Also the level of 13,14-dihydro-15-keto-PGF$_{1\alpha}$ (M-PGF$_{2\alpha}$, a metabolite of PGF$_{2\alpha}$) was measured by similar radioimmunoassay. The recovery of M-PGF$_{1\alpha}$ (100–200 pg/ml) added to the amniotic fluid was 84·6% ($n = 10$).

The t-test for paired and unpaired observations and linear regression analysis were used for the statistical treatment of the results.

Results

Each amniotic fluid sample contained immunoreactive 6-keto-PGF$_{1\alpha}$, TxB$_2$ and M-PGF$_{2\alpha}$, but they were not related to the L/S ratio, or the presence of phosphatidylglycerol (Table 2). No consistent changes in 6-keto-PGF$_{1\alpha}$, TxB$_2$ and M-PGF$_{2\alpha}$ took place in the women whose L/S ratio increased from below 2 to more than 2 ($n = 16$) or whose phosphatidylglycerol became detectable during the serial sampling ($n = 19$) (Table 3).

The level of 6-keto-PGF$_{1\alpha}$ correlated with that of TxB$_2$ (r = 0 398, P<0 001, n = 78) and M-PGF$_{2\alpha}$ (r = 0 529, P<0 001, n = 71), whereas no relation was seen between the amniotic fluid TxB$_2$ and M-PGF$_{2\alpha}$ (r = 0 224, P>0·05, n = 71).

Discussion

Several experimental and clinical data suggest the significance of various prostanoids in fetal lung maturation (Colacicco *et al.* 1977; Powell & Solomon 1978, 1980; Oyarzya & Clements 1978; Kitterman *et al.* 1981). Prostaglandin E$_2$ and PGF$_{2\alpha}$ stimulated the incorporation of choline and palmitate into lecithin in cultured human lung cells (Colacicco *et al.* 1977); arachidonic acid is converted to classic

Table 2. Amniotic fluid levels of 6-keto-PGF$_{1\alpha}$, TxB$_2$ and M-PGF$_{2\alpha}$ in women with different lecithin/sphingomyelin ratios

Prostanoid	Lecithin/sphingomyelin ratio		
	<2	2	>2
6-keto-PGF$_{1\alpha}$ (pg/ml)	37 6 (15 6) ($n = 16$)	34·5 (7 9) ($n = 15$)	40 9 (18 0) ($n = 47$)
TxB$_2$ (pg/ml)	27 0 (13 7) ($n = 16$)	32·6 (12 5) ($n = 15$)	39 2 (26 7) ($n = 46$)
M-PGF$_{2\alpha}$ (pg/ml)	99 8 (46 2) ($n = 15$)	99 6 (33 0) ($n = 15$)	118 4 (62 7) ($n = 42$)

Results are means (SD).

Table 3. Amniotic fluid levels of 6-keto-PGF$_{1\alpha}$, TxB$_2$ and M-PGF$_{2\alpha}$ in the samples with detectable and undetectable phosphatidylglycerol

Prostanoid	Phosphatidylglycerol Undetectable All samples	 Last samples	 Detectable
6-keto-PGF$_{1\alpha}$ (pg/ml)	38·9 (16·8) ($n = 59$)	36·5 (12·6) ($n = 19$)	39·2 (14·6) ($n = 19$)
TxB$_2$ (pg/ml)	33·4 (16·8) ($n = 59$)	37·9 (19·9) ($n = 18$)	42·0 (28·8) ($n = 18$)
M-PGF$_{2\alpha}$ (pg/ml)	105·1 (45·0) ($n = 56$)	88·6 (41·9) ($n = 16$)	129·4 (78·7) ($n = 16$)

Results are means (SD).

prostanoids, 6-keto-PGF$_{1\alpha}$ and TxB$_2$ by homogenates of fetal rabbit and bovine lungs (Powell & Solomon 1978); and amniotic fluid levels of some prostanoids increased with advancing fetal age (Satoh *et al.* 1979; Ylikorkala *et al.* 1981). Furthermore, prostaglandins and PGI$_2$ stimulated adenylate cyclase activity in lungs from fetal rabbits (Powell & Solomon 1980), which suggests that pulmonary prostanoids could enhance cyclic AMP synthesis and thereby stimulate surfactant formation, which is a cyclic AMP-dependent event (Hallman 1977; Gross & Rooney 1977). Glucocorticoids, known stimulators of lung maturation (Liggins & Howie 1972), may also operate through PG-induced increase of cyclic AMP, since they stimulated PG synthesis in fetal rat lungs (Tsai *et al.* 1983) and raised the level of lung cyclic AMP (Barrett *et al.* 1976). That vaginal delivery is accompanied by increased PG release in various fetoplacental tissues (Liggins *et al.* 1977) and amniotic fluid (Keirse *et al.* 1977; Mitchell *et al.* 1978, 1979), and by a certain protection against RDS of the newborn, also suggests a possible association between prostanoids and fetal pulmonary maturation. Furthermore, infants with established surfactant deficiency are characterized by various abnormalities in classic PGs and PGI$_2$ (Ylikorkala *et al.* 1984).

In view of the intimate contact between fetal lungs and amniotic fluid it was thought that the amniotic fluid M-PGF$_{2\alpha}$, 6-keto-PGF$_{1\alpha}$ and TxB$_2$ might reflect, at least to some degree, the formation of the respective parent compounds by the fetal lungs. Further support for this expectation came from the data that prostaglandins are involved in the flux of surfactant in fetal lambs (Kitterman *et al.* 1981) and that 6-keto-PGF$_{1\alpha}$ and TxB$_2$ were detected in the tracheal fluid of fetal sheep (Mitchell & Robinson 1978). However, we present here the first in-vivo evidence that amniotic fluid PGs are not related to fetal lung maturation in man. This may suggest that pulmonary PGF$_{2\alpha}$, PGI$_2$ and TxA$_2$ are not significant for fetal lung maturation. It is also possible that fetal lungs contribute so little to the total amniotic fluid prostanoids, that a relation between the amniotic fluid surfactant and prostanoids, even if it existed, may not have been detected in a study like ours. Regardless of the origin of the amniotic fluid M-PGF$_{2\alpha}$, 6-keto-PGF$_{1\alpha}$ and TxB$_2$ (fetoplacental tissue, fetal lungs and urine), we can at least conclude that their measurements are useless in the assessment of human fetal lung maturation.

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The 'birth plan' experience

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Summary. All antenatal patients booked for hospital confinement in Huddersfield have been offered a 'birth plan' on which to indicate their wishes regarding labour ward procedures. The first 100 plans have been analysed and the information supplemented by a questionnaire answered by the women in the puerperium.

Childbirth must be as safe as possible but should also be a rewarding and fulfilling experience for the mother. When the delivery proves emotionally satisfying it can have a positive impact upon the future mother–child relationship. Over the last few years, however, maternity units have been increasingly criticized for 'high technology' obstetrics which it is claimed takes away the woman's freedom and makes the birth less enjoyable. Zajicek (1980) stressed that the attendant staff should be as aware of the woman's psychological and physical comfort as of the potential medical dangers and problems which might occur. Unfortunately some patients fear that this does not happen in the busy environment of a sophisticated modern obstetric unit and as a result they may reject hospital confinement.

In Huddersfield over 99% of all deliveries take place in two maternity units run by consultants each handling about 1500 deliveries per year. Indeed the House of Commons Social Services Committee (1980) (Short Report) recommended that deliveries in small units and home deliveries should be reduced even further. This trend towards more deliveries in larger units has reduced perinatal mortality and should make the patient feel safe and relaxed knowing that she is in the hands of experienced staff. Inevitably hospitals lack the comfort and freedom of the patient's own home and may be seen as a hostile environment. To help overcome this a 'birth plan' was introduced in June 1982 and offered to all antenatal patients (see Appendix).

The idea was to give the woman a chance to consider the various events which might occur in labour and to help her to express her own wishes.

All patients in Huddersfield are visited at home by a community midwife early in the third trimester and this was the time chosen to offer the 'birth plan' together with an explanation of the listed procedures. Those patients who wished to use the 'birth plan' returned it at their routine antenatal clinic visit and thereafter it was kept in the patient's hospital case notes. On admission in labour, the 'birth plan' was studied by the midwife supervising the labour and then attached to the patient's partogram so as to be obvious to all her attendants.

Patients and methods

A study was made of the first 100 English speaking patients who gave birth after completing a 'birth plan'. The patients were also interviewed within 48 h of delivery by one of us (C.E.O.E.) and asked to complete a questionnaire on their experiences with the 'birth plan'.

The 100 patients included 56 women experiencing their first delivery, and 44 multiparous women with between 1 and 4 previous deliveries (mean 2·5). The primiparous patients were aged between 18 and 36 years (mean 25 1) and the multiparous ranged from 19 to 42 years (mean 28·5).

Labour began spontaneously in 72% of the patients, 27% had labour induced and one woman had an elective lower segment caesarean section. A normal vertex delivery occurred in 81% and 9% were delivered by forceps. Breech delivery occurred in 4% and 6% had a lower segment caesarean section in labour. There were no significant differences in these rates between the primiparous and multiparous groups and

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there were no multiple pregnancies or perinatal deaths.

Pethidine was required by 66% of the primiparous patients and only 18% of the multiparous group; 77% of the primiparous and 82% of the multiparous patients had gas and oxygen (Entonox) whilst only 3% had epidural analgesia. The mean duration of labour in the primiparous group was 9 h 10 min (range 2 h 26 min to 23 h 5 min) and in the multiparous group it was 4 h 35 min (range 40 min to 10 h 50 min). Seven babies were admitted to the special care baby unit, six of them were returned to their mothers within 24 h and only one stayed for 3 days.

Results

The wishes expressed on the birth plan are shown in Table 1 listed separately for the 56 primiparous and the 44 multiparous patients. There were, however, no obvious differences between the responses from these two groups.

There was considerable interest in the plan and it was well received by those who used it as shown by the summary of the postnatal questionnaire given in Table 2. Most patients seemed to find the plan 'helpful' and 'reassuring'. Two patients scored the plan as being of no value, one indicated that it was 'too complicated' and the other stated that 'doctors and nurses know what is best for each individual patient'. One multipara with a completely normal delivery indicated that the plan caused 'anxiety' but unfortunately gave no further details. In fact several multiparae commented that the plan appeared too difficult for mothers having their first baby but none of the primiparous group stated that this was a problem.

Table 1. Patients' responses on 100 'birth plans' completed in the antenatal period

	Would like			No strong views			Wish to avoid		
	Primiparous	Multiparous	Total	Primiparous	Multiparous	Total	Primiparous	Multiparous	Total
On admission in labour									
Partial shave	16	17	33	33	22	55	7	3	10
Enema	7	8	15	28	18	46	17	15	32
Presence of partner/relative/friend	47	24	71	5	9	14	4	10	14
Wearing own nightdress	3	1	4	17	15	32	36	24	60
During labour									
Continuous monitoring of baby's heart rate by electronic machine	11	12	23	33	22	55	9	5	14
Correcting an unduly slow labour by rupture of the membranes (breaking the waters)	13	12	25	33	20	53	5	8	13
Correcting an unduly slow labour by an intravenous infusion (drip)	8	9	17	37	17	54	10	14	24
Presence of partner/relative/friend	54	34	88	2	6	8	0	3	3
Pain control									
Pethidine or other drugs by injection	14	11	25	25	18	43	15	12	27
Gas and oxygen by face mask	28	24	52	24	10	34	2	6	8
Epidural (not always available)	2	2	4	8	4	12	40	33	73
Delivery									
Presence of partner/relative/friend if normal delivery	52	34	86	3	6	9	0	3	3
Presence of partner/relative/friend if complications with delivery (e.g. forceps)	40	32	72	9	5	14	6	7	13
Episiotomy	4	2	6	28	18	46	16	17	33
Nursing baby immediately	49	38	87	7	5	12	0	0	0
Putting baby to breast as soon as possible	46	29	75	8	6	14	1	4	5

Totals for each item are less than 100 because some patients did not tick every section.

Table 2. Replies made in the puerperium to the questionnaire about the 'birth plan'

	Very good	Good	No value	Bad	Very bad
Patient's opinion of plan	75	23	2	0	0
Partner's opinion (13 not consulted)	47	34	6	0	0
	All	More than half	Half	Less than half	None
Amount of plan ticked	89	9	0	2	0
Amount of plan fulfilled	55	38	4	3	0

Replies to request for patient to ring any of the following which reflected her feelings about the plan

Helpful	79	Frightening	0	Too complicated	2
Too simple	3	Reassuring	61	Cause anxiety	1

Should the plan be altered?	Yes	18	No	82

Several patients asked for more details of the procedures mentioned and 18% suggested alterations in the plan. Suggestions for additional choices in the plan included natural delivery of the placenta, time of cord clamping, presence of students, restriction of postnatal visitors and postnatal feeding wishes. One mother suggested that episiotomy should be deleted as she could not envisage anyone indicating a wish for this.

Space was left on the questionnaire for free comments and when utilized these were all very encouraging. One woman wrote 'I was made to feel that I was a complete individual and due to this put all my trust in the members of staff'. Another commented 'Until seeing everything listed, I didn't realize that there was so much involved in having a baby and that I had options on the way the labour and delivery was handled. Things that I was unsure about, the midwife made very clear and if it hadn't been for this plan, I wouldn't have thought to ask about various procedures.'

Discussion

Our initial experience with the 'birth plan' in our hospital has been extremely favourable. Before the plan had been introduced some patients had prepared their own lists of likes and dislikes and most of these were very reasonable. Some, however, appeared as rigid demands presented in an almost antagonistic manner and as these were usually produced on admission in labour discussion of the list was restricted. The danger of this was that when an alternative course of action became necessary the patient was totally unprepared and accepted it with a sense of failure. Sadly some women mar the satisfaction of childbirth by setting themselves unrealistic and inflexible targets which are not fulfilled.

By providing a birth plan we have endeavoured to demonstrate our desire to recognize the wishes of our patients. The plan expresses our intention to be flexible and on the 'same side' as the mother-to-be, an attitude encouraged by the RCOG (1982).

Many procedures undertaken in a labour ward have very little obstetrical significance, for example having a partial shave. There were 33 women who wished to be shaved and 10 who did not want to be shaved, and we were able to comply completely with these wishes. For the 55 women with 'no strong views' and the two who did not tick this item the decision was made after discussion with the patient on her admission in the routine manner. Other items, such as continuous fetal heart rate monitoring, could be of great importance in labour. Here the plan provided two benefits. First, it revealed a group of 23 women who wanted to have fetal heart monitoring and therefore they could be monitored throughout labour. This was in keeping with Molfese *et al.* (1982) who showed that women in Illinois have a positive response to intrapartum fetal monitoring. Second, it enabled a proper discussion of the procedure to be undertaken in the antenatal period which made explanation easier when action in labour became advisable on obstetrical grounds, even when this was contrary to the originally expressed wish of the patient.

Our results showed that 25 women were willing to have an unduly slow labour corrected by rupture of the membranes with 13 opposing this procedure. Intervention in labour is a widely debated topic in the lay press and its opponents are perhaps the more vociferous. The use of a 'birth plan' and the discussion that goes with it could help to put procedures such as this in a true perspective. Even so there is obviously a preference towards avoiding an intravenous infusion. The numbers wishing to have and those wishing to avoid pethidine were almost equal but more wanted gas and oxygen and most of them rejected epidural analgesia.

Epidurals are not widely used in Huddersfield and only three patients in this series had epidural analgesia. Perhaps our population has had little experience of epidural analgesia and so had no informed view, but Morgan *et al.* (1982) have shown that even when epidurals are available for all it is rejected by 46%.

We were surprised that six women indicated that they would like an episiotomy. This was a desire of which we had not previously been aware and seemed to stem from a fear of uncontrolled tearing. In practice reassurance at the time of delivery proved sufficient and no episiotomies were performed unless there was an indication. Nevertheless it was helpful for the midwives to know that the patient had this particular anxiety.

Of the women who completed the 'birth plan' antenatally, 89% marked all sections. We explained to the patients that a flexible approach is always necessary in labour but even so 55% had all their wishes fulfilled. Only 7% felt they had achieved half or less and four of these had significant obstetrical complications requiring intervention including two who had a caesarean section. The results from the patients' point of view were therefore good. Initially there was some anxiety that the midwife's role would be undermined but our experience has been to the contrary in that use of the plan leads the patient to have a greater confidence in the staff.

Approximately one in five of our antenatal patients filled in a 'birth plan'. This ratio may well increase if the current trend continues towards greater involvement by patients in decisions relating to their obstetrical management. However, in this survey a high proportion had 'no strong views' concerning the more technical aspects such as fetal monitoring, augmentation of labour and episiotomy and seemed happy to leave these decisions to their professional attendants.

We intend to continue using the plan but to keep its contents under review. We have resisted the requests for more explanation on the plan about the procedures as we feel this should be by discussion between the patient and her midwife or doctor. The 'birth plan' must not become an alternative to normal antenatal education. It would be possible to include antenatal and postnatal events but this would make it somewhat cumbersome. Moreover, it is during labour that the woman feels she will be at her most vulnerable and least able to make decisions and as such this is where a 'birth plan' has its greatest impact.

Acknowledgments

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APPENDIX

Huddersfield Maternity Unit—'birth plan'

This birth plan is designed for those expectant mothers who wish to record their preferences about various aspects of maternity care. Although you are booked under the care of a consultant who provides overall supervision you will inevitably see many different midwives and doctors when you attend the clinics and come into hospital. If you complete all or any part of this plan it will be kept in your hospital case notes so that all the staff know your views. Every effort will be made to observe your wishes but if this is not possible the staff will explain the reasons to you.

Remember the staff both in the clinics and on the wards are there to make your pregnancy as safe and as happy as possible. When you have any queries please ask any of the midwives or doctors. If there is any cause for concern when at home feel free to telephone the hospital where you are booked to have your baby and speak to the sister on the labour ward who will be happy to advise you. Any procedures such as antenatal tests, induction of labour, pain relieving injections should only be performed after a full explanation has been given and you have indicated your approval. If you do not fully understand why something is being done please ask.

Four ways of avoiding problems

1. *Make your first visit to the antenatal clinic as early as possible in your pregnancy.* The screening tests and medical examination may reveal health problems about which action needs to be taken before the major changes of pregnancy occur. There are also some pregnancies where special tests or treatments need to be undertaken in the early weeks to ensure a satisfactory outcome.
2. *Keep your clinic appointments.* If you are unfortunate and have a pregnancy complication this can usually be recognized at a stage before serious harm develops. You can then be advised what steps to take to avoid a major problem.
3. *Tell the staff of any health problems.* Two months before the baby is due you will be given a chart on which to record your baby's movements. It is important to follow the instructions carefully or early evidence of stress on the baby may be missed. You should report at once if there is any vaginal bleeding in pregnancy or if the membranes rupture (waters break) or if labour contractions occur more than 3 weeks before your expected date of delivery as any of these could have serious consequences.
4. *Attend the hospital as soon as you commence in labour.* If possible telephone first so that they can prepare for you. If the baby has been under any stress then the first few hours of labour may be critical and a careful observation must be kept on the baby's heart rate and position. A very slow labour may cause complications with the actual delivery. For this reason it may be advisable to correct an unduly slow labour by having the membranes ruptured (waters broken) or by an intravenous infusion (drip).

Put a tick against any of the following to indicate your own views.

	Would Like	No Strong Views	Wish to Avoid
On admission in labour			
Partial shave			
Enema			
Presence of partner/relative/friend			
Wearing own nightdress			
During labour			
Continuous monitoring of baby's heart rate by electronic machine			
Correcting an unduly slow labour by rupture of the membranes (breaking the waters)			
Correcting an unduly slow labour by an intravenous infusion (drip)			
Presence of partner/relative/friend			
Pain control			
Pethidine or other drugs by injection			
Gas and oxygen by face mask			
Epidural (not always available)			
Delivery			
Presence of partner/relative/friend if normal delivery			
Presence of partner/relative/friend if complications with delivery (e.g. forceps)			
Episiotomy			
Nursing baby immediately			
Putting baby to breast as soon as possible			

Comments (Please add any further special wishes you would like the staff to consider.)

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Intraperitoneal bleeding from ectopic decidua following hormonal contraception. Case report

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Case report

A 42-year-old Chinese woman was admitted on 23 January 1984 because of right lower abdominal pain for 1 day and secondary amenorrhoea for 9 months. Her previous menstrual history was normal with 30-day cycle and 5-day flow. She had had two normal vaginal deliveries and two induced first trimester abortions. She received 3-monthly injections of medroxyprogesterone acetate 150 mg beginning immediately after her second abortion on 15 March 1983. She remained amenorrhoeic till 29 November 1983 when she changed to the oral combined contraceptive, Microgynon (21 tablets of 0 15 mg levonorgestrel and 0 03 mg ethinyloestradiol). She had no withdrawal bleeding after two courses of Microgynon, the last of which was completed 1 week before her admission.

On admission, the patient was afebrile with blood pressure of 130/90 mmHg and pulse rate of 85/min. Abdominal examination showed marked tenderness over the right lower quadrant with guarding and rebound. An irregular tender mass of 4–5 cm in diameter was palpated through the right vaginal fornix. The haemoglobin was 13 0 g/dl and the white cell count was normal. A pregnancy test on urine was negative. A pelvic ultrasonic scan showed an empty uterus and a right adnexal mass. The clinical diagnosis was ectopic gestation with pelvic haematocele.

Emergency laparotomy showed an engorged right fallopian tube which was adherent to the right ovary, the back of the uterus and the pelvic wall. A haematocele measuring 5 cm in diameter was found on the right side of the pouch of Douglas. The uterus, left fallopian tube and ovary were normal. There was no obvious endometriosis or pelvic inflammatory disease. Diagnosis at operation was right tubal abortion with pelvic haematocele. Right salpingo-oophorectomy and evacuation of the haematocele were performed. Total blood loss was estimated to be 400 ml. The postoperative course was uneventful.

The operation specimen was a fallopian tube measuring 3 cm in length with no rupture site. There was a haemorrhagic swelling, 2 cm in diameter, just proximal to the fimbrial end. Histologically, there was extensive decidual tissue with haemosiderin deposits on the serosa of the fallopian tube. No chorionic villi or trophoblastic tissue was detected in the whole fallopian tube. The ovary was normal. The pathologist's diagnosis was bleeding ectopic decidual reaction with pelvic haematocele formation.

Discussion

Decidual reaction is an exaggeration of normal response of the endometrium to progesterone (Novak & Woodruff 1974). It has also been described in many ectopic sites other than the uterus such as in the fallopian tubes, ovary, cervix, vagina, cul-de-sac, appendix, omentum and the peritoneum of small intestine and is sometimes known as deciduosis peritonei (Kwan & Pant 1964; Jeffcoate 1975). The aetiology and significance of this ectopic decidual reaction is unknown. The possibility of hormonally induced metaplastic changes in the subcoelomic pluripotent mesenchyme and in areas of inflammation and previous endometriotic deposits of the peritoneum have been suggested but not substantiated (Tilden & Winstedt 1943). In the absence of pregnancy, ectopic decidual changes have been attributed to the stimulation of appropriate cells by progesterone, progesterone-like substances from the corpus luteum or the adrenal cortex (Ober *et al.* 1957).

Intra-abdominal haemorrhage secondary to severe ectopic reaction of the peritoneal surface has been reported as rare occurrence in late pregnancy (Melody 1950; Doyle & Phillips 1957), during labour (Rogers & Seckinger 1965) and in the puerperium (Hulme-Moir & Ross 1969; Sabautelle & Winger 1973; Richter *et al.* 1983). We report the first case of bleeding ectopic decidual reaction from the serosal surface of the fallopian tube in the absence of pregnancy in a woman who received a long-acting injectable progestogen contraceptive. Such a complication has never been mentioned before as a possible side effect of progestogen administration (Hawkins & Elder 1979; Population Reports 1983).

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A partial hydatidiform mole, dispersed throughout the placenta, coexisting with a normal living fetus. Case report

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Case report

The third pregnancy of this 23-year-old patient was uneventful until the 16th week, when she had a traffic accident. Two days later she had vaginal blood loss and came to the out-patient clinic. Ultrasound investigation (real-time scanner) revealed a normal pregnancy. Just above the internal cervical os a trans-sonic space with a diameter of about 5 cm was observed and interpreted as a blood clot; it was seen on weekly ultrasound examination until the 27th week, while the fetus was developing normally. In the 27th week of the pregnancy ultrasonographic scanning revealed a hydropic placenta with a thickness of 6 cm. Two days later early fetal hydrops (ascites, subcutaneous oedema) was observed (Fig. 1).

Amniotic fluid obtained by amniocentesis was found to contain meconium and methaemalbumin. From the Kleihauer-Betke test a feto-maternal transfusion of about 80 ml fetal blood was estimated.

The diagnosis of severe fetal anaemia, probably resulting in fetal hydrops, was discussed with the parents and the paediatrician. When signs of fetal distress occurred in the fetal heart rate pattern (unreactive with spontaneous decelerations) intra-uterine transfusion was considered but rejected since the fetus was lying with its back directly anterior. It was decided to deliver the fetus by caesarean section and a female infant, weighing 980 g, was born. The Apgar score at 5 min was 3, the pH of the umbilical artery blood was 7·16. The infant macroscopically had no congenital anomalies, but was very pale; blood haemoglobin concentration was 6·4 g/dl.

Neonatal problems were frequent (anaemia, hypoglobulinaemia, oedema) but after an exchange blood transfusion the main difficulty was a severe respiratory distress syndrome. After 67 days of mechanical ventilation it proved impossible to keep the baby adequately oxygenated, ventilation was stopped and the baby died; the parents did not consent to an autopsy. The karyotype revealed a 46XX pattern.

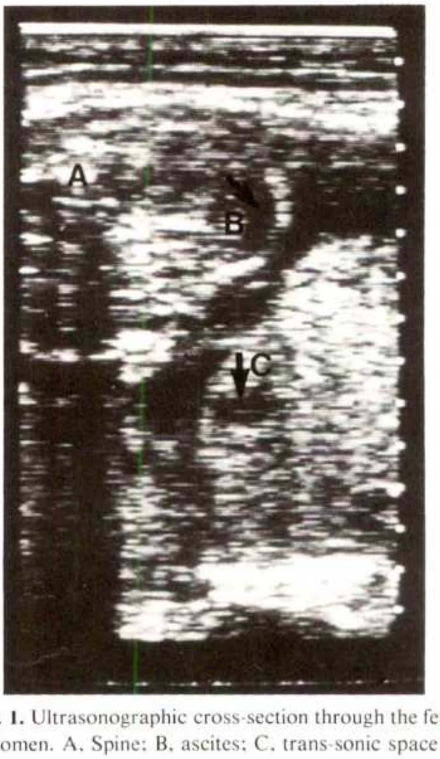

Fig. 1. Ultrasonographic cross-section through the fetal abdomen. A, Spine; B, ascites; C, trans-sonic space in the placenta.

Macroscopic examination of the placenta, weight 960 g, revealed cystic villi dispersed throughout the placenta and macroscopically characteristic of partial mole (Fig. 2). After fixation the placenta weighed 330 g. The macroscopically vesicular villi (Fig. 3) showed considerable hydatidiform degeneration with surface proliferation of cytotrophoblast and syncytiotrophoblast (Fig. 4). In these areas the

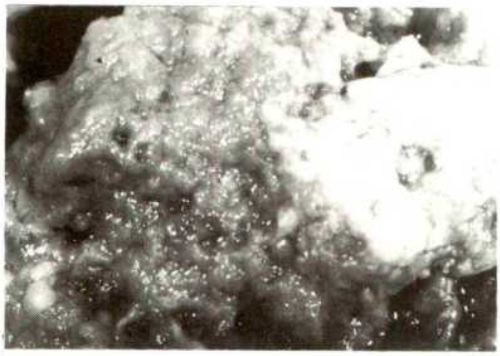

Fig. 2. Macroscopic view of the placenta with clearly recognizable cystic villi.

proliferation showed anisokaryosis, but there were no signs of increase of the nucleolar size. The cytoplasmatic borders were locally indistinct. The remainder of the placental tissue showed no abnormality and there were no signs of villitis.

Discussion

The incidence of partial mole coexisting with a viable fetus is low. In the Netherlands the frequency of partial mole without evidence of triploidy was 1 in 50 000 pregnancies and 1 in 22 000 deliveries in 1978 and 1979 (Franke 1983).

In the international literature only 18 cases have been described of pregnancies with coexisting moles which ended in the delivery of a live infant (Yee *et al.* 1982). We deliberately bypass the obstetric and neonatal aspects of this case report and wish to focus on the unexpected finding of a dispersed partial mole with a normal karyotyped living fetus.

The histological diagnosis was made according to the criteria of a partial mole as given by Franke (1983): 'in addition to some parts of normal pregnancy (fetus, embryo, amnion, chorion) there are molar cysts with a relatively moderate trophoblastic proliferation and with or without morphological evidence of triploidy'. The trophoblastic proliferation is clearly demonstrated in Fig. 4.

The complete hydatidiform mole usually becomes manifest through vaginal blood loss early in pregnancy and by the absence of fetal heart sounds. Ultrasound examination usually gives the diagnosis. By contrast, the partial mole does not necessarily result in vaginal blood loss. Especially in combination with a viable fetus, it is more difficult to detect by ultrasound because of the internal haemorrhage and blood clots that often occur. In those cases the classic speckling or 'snowstorm effect' does not appear.

Only 35% of moles are partial and of these only one in three contain fetal parts. In the literature only one case of a normal karyotyped 46XX mole with a normal fetus has been described (Szulman & Surti 1978), and the

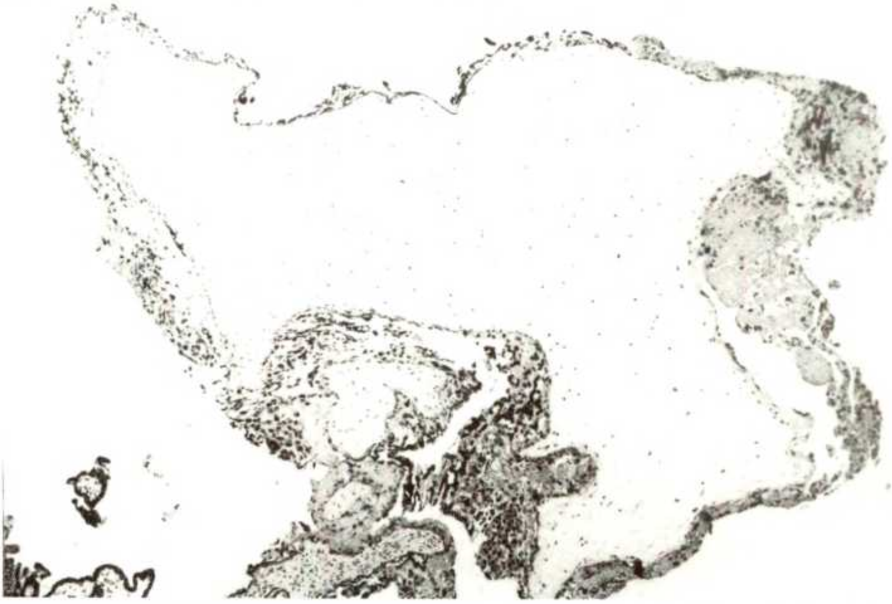

Fig. 3. Villus with oedematous avascular stroma and proliferation of trophoblast. H&E, ×33.

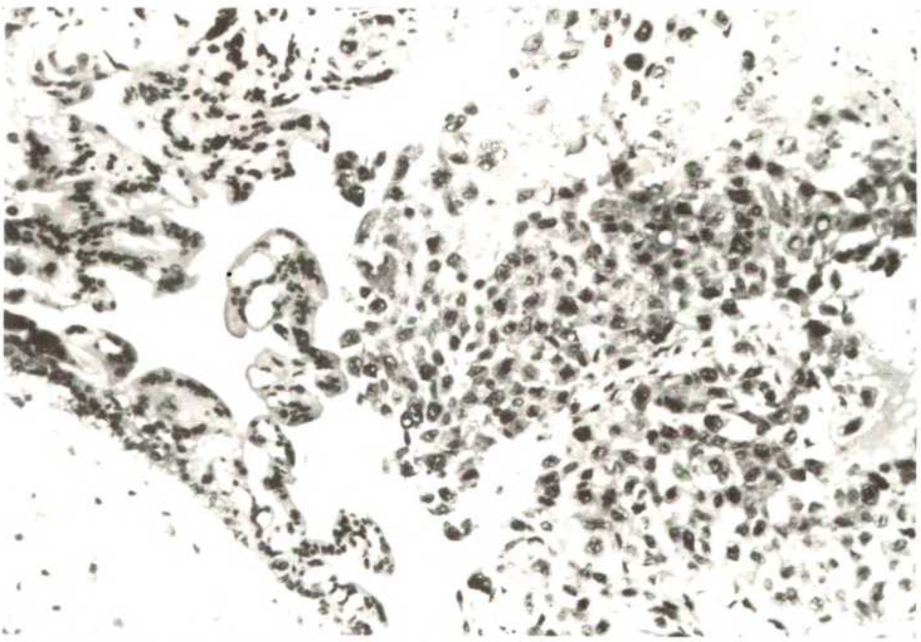

Fig. 4. Part of hydropic villus on the left with trophoblastic proliferation (detail of Fig. 3).

authors considered this as a possible third form of hydatidiform mole. Recently a case report of a normal term fetus was published (Hartfield 1983) but careful reading reveals that this was not a hydatidiform mole since there are no proliferative changes; the author described a hydropic degeneration.

In a recent publication it was stated that all partial moles are triploid (Szulman *et al.* 1981), but since a karyotype of the mole presented here could not be obtained, we can neither confirm nor deny this statement. Histological examination confirmed the diagnosis of molar tissue, but histological evidence of triploidy was not seen.

Although some authors state that there are no choriocarcinomas following a partial mole, Franke (1983) described a patient with persistent trophoblastic disease after evacuation of a partial mole. He therefore suggested that β-hCG levels should be monitored in the maternal serum until they decreased to less than 2 ng/ml. In our patient the β-hCG levels were 2800 ng/ml on the day of the delivery and decreased to less than 2 ng/ml 51 days later.

From this presentation it is evident that partial mole may present itself differently from the manner hitherto described, with molar tissue dispersed between normal villi. Vaginal blood loss in combination with 'trans-sonic spaces' in or near the placenta on ultrasound examination should raise suspicion of partial mole. In that case a Kleihauer-Betke test should exclude or confirm feto-maternal blood transfusion. Following delivery, maternal β-hCG levels should be monitored until the plasma level decreases to less than 2 ng/ml.

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CORRESPONDENCE

Failure of post-coital contraception after insertion of an intrauterine device. Case report

Dear Sir,
The case report of Kubba & Guillebaud [*Br J Obstet Gynaecol* (1984) **91,** 596–597] is used to argue the case that the failure rate from this method is the same as that which would be expected for the intrauterine contraceptive device (IUCD) in general.

He quotes an earlier work of ours (Black *et al.* 1980) but does not mention a more recent paper on delayed post-coital IUCD insertion (Goldstuck 1983) which provides even stronger evidence of the powerful effect of the IUCD when used in this manner. In addition to these nearly 300 reported cases we have inserted more than 1000 other post-coital IUCDs and have not had a single failure. Although our records are not complete we know of no later failures in post-coital IUCD users.

The post-coital IUCD appears to have a very powerful anti-fertility effect, which appears to be independent of the type of device used and the clinic fitting it. This is not the same as for IUCD use in general where there is marked variation between results in different clinics. This is all the more unusual because IUCD failure is normally higher in the earlier cycles of use as the authors explain. Our post-coital insertions were performed by both experienced and inexperienced inserters and included women who had had multiple coitus during the treatment cycle.

This, and other early IUCD problems might possibly be explained by a central IUCD effect such as endorphin release causing temporary infertility. We are at present investigating this possibility.

Norman Goldstuck
Marie Stopes House
Well Women Centre
London W1P 6BE

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Black, T. R. C., Goldstuck, N. D. & Spence, A. (1980) Post-coital intrauterine device insertion—a further evaluation *Contraception* **22,** 653-658.

Goldstuck, N. D. (1983) Delayed post-coital IUD insertion. *Contraception Delir Syst* **4,** 293-296

Authors' reply

Dear Sir,
We agree with Dr Goldstuck about the high efficacy of IUCDs used for post-coital contraception. Of the 1300 cases we referred to, in our case report, in fact over 700 cases were from Marie Stopes House (T. Black, Personal Communication). The case we reported is, therefore, still numerically compatible with the quoted failure rates of IUCDs in general. A central effect following IUCD insertions is unlikely, on its own, to account for the very high efficacy of postcoital IUCDs. Indeed, previous reports of a central effect hypothesize a more persistent rather than temporary mode of action (Blum *et al.* 1983). We await Dr Goldstuck's investigation of this mechanism with interest.

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John Guillebaud
Medical Director
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London W1 5TW

Reference

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British Journal of Obstetrics and Gynaecology
January 1985, Vol. 92, pp. 108–112

BOOK REVIEWS

Principles and Practice of Clinical Gynecology edited by N. K. Kase & A. B. Weingold. Wiley, New York, 1983, 1099 pages, with figures and tables, £53.30

This monumental work will surely become a classic. It covers the entire spectrum of modern gynaecological practice, from the management of rape to in-vitro fertilization. Such encyclopaedic range justifies the book's considerable length; judicious editing has ensured that individual sections are concise, relevant and clear. An enviable uniformity of style has been achieved by the use of several contributions from selected authors. Forty-eight of the sixty-five chapters were written by seven of the twenty-two contributors, and no less than twenty-eight by the editors themselves. Such economy could have resulted in superficial accounts of some topics, but no such criticism of this book is justified. Subjects are discussed in a depth sufficient to provide plentiful information for the general gynaecologist, while recent trends are carefully documented for those with special interests. Many chapters include references to articles published less than 12 months before the text, attesting the organizing skills of editors and publishers alike. But the book is more than a collection of meticulous essays. New ideas abound. Essential but traditionally uninspiring topics such as pelvic anatomy are revivified by Weingold's imaginative presentation using photographs of surgical operations, sonar and CT scans, and contrast radiography. Accounts of hormones and their production are enlivened by a succinct account entitled 'How hormones work: hormones and receptors'. Useful chapters such as 'Genetics for gynecologists' and 'Special considerations in medical management of female patients' are interposed within what amounts to a monograph by Kase upon reproductive endocrinology (male as well as female). Gynaecological malignancy is covered in a concise and workmanlike manner by Lucas, Ballon and Jones and family planning by Elizabeth Connell. The editors point out rather self-consciously that seven of the authors are women. If justification were required for what they appear to consider a significant innovation, it is amply provided by a spirited account of 'Women in modern society'. This excellent section comprises chapters on gender identity, sexuality and rape as well as a comprehensive review of legal issues which, although American in emphasis, covers many situations relevant to British clinical practice. No gynaecological reference library should lack a copy of this splendid textbook. Our own copy will be firmly chained to the wall!

W. Dunlop

Drug Prescribing in Pregnancy. No 7 in Current Reviews in Obstetrics and Gynaecology by Beatrice Krauer, Felix Krauer & Frank Hytten. Churchill Livingstone, Edinburgh, 1984, 188 pages, with figures and tables, £9.95 and **Drug Use in Pregnancy** Leo Stern. Adis Health Science Press, Australia, 1984, 281 pages illustrated with figures, tables and photographs, £29.50

Despite similar titles, these two books are strikingly different. That edited by Stern is a larger, heavier book, consisting of a series of review articles by different authors, 11 chapters from the US, one from Holland and one from France. That by Krauer, Krauer and Hytten is not a multi-author production but a beautifully written well-balanced, light and informative text. If you are a busy clinician who doesn't want to read any further than the first paragraph of this review, but who would like advice on drug prescribing in pregnancy, let me say at once that Krauer, Krauer and Hytten is the one you should buy. Before dealing with each in more detail, I should mention however two minor criticisms that apply to both. Neither discusses the management of pre-eclampsia in any detail, nor the effects of drugs used in this context on the outcome of pregnancy. Neither text in my opinion explains correctly the principles of placental drug transfer, though Krauer, Krauer and Hytten come nearer. Both quote the same archaic equation, which actually relates to the velocity of movement across a membrane, not the rate of drug transfer from mother to fetus. The equation (mentioned twice in Stern) ignores the effect of flow *and* protein binding on either side of the membrane, and contains a constant which to my knowledge has never been calculated for any drug—indeed it would be impossible. Moreover neither text differentiaties the *rate* of drug transfer from the *equilibrium* fetal/maternal concentration ratio. Both books quote as evidence of transfer rate the time taken for drug to appear in fetal circulation. This merely reflects, of course, the maternal dose rate and placental flow, and the sensitivity of the assay technique.

In *Drug Use in Pregnancy*, edited by Stern, the language is verbose; the editor's introduction gives us a foretaste in describing fetal development as 'a series of longitudinal maturational events . . .', and no infinitive goes unsplit. The book contains, despite its length, no general outline of pharmacokinetics of pregnancy, but a wealth of inconsistent data, with little attempt to reconcile or interpret them. Chapter 1 on ethical and legal implications and chapter 2 on regulatory agencies, clearly overlap subject matter, though the latter, by Lasagna, is good. Chapter 3, on drug-metabolizing enzymes, is packed with data, much referring to non-pregnant adults, and contains the term 'elimination *time*'. This has no meaning. Chapter 4, on placental transfer, conveys little basic understanding of the subject, and (apart from the general criticisms already mentioned above) for example contains the phrase 'highly ionized molecule'—a molecule is either ionized or not! Pethidine is said to be a highly potent analgesic—it is of course just about the least *potent* we have. Digitalis is said to equilibrate in mother and fetus in 15 minutes—which would be an impossible feat for the most diffusible drug. Concentration ratios are sometimes quoted M/F and sometimes F/M. The next four chapters, on mechanisms of teratogenesis, malformations in man, anticonvulsants and drug abuse respectively, all include overlapping information on teratogenesis. Single case reports are repeatedly cited as if they were evidence of teratogenesis. Breast feeding is said to be contraindicated with anticonvulsant medication (overlooking the problems of neonatal withdrawal, and the way in which these can be mitigated by breast feeding, quite apart from the other benefits). The teratogenic potential of diazepam is quite surprisingly dismissed and alcohol intake is referred to in oz and ml on the same page. Chapter 9 on diabetes, quite unlike the foregoing, deals with the disease itself, is brief and well-informed, but makes no mention of drug effects. Chapter 10, on management of chronic disease, mentions the effects of indomethacin on labour and the neonatal circulation without any explanation of their common mode of action. In proscribing cimetidine in pregnancy the authors seem unaware of its wide and apparently safe use in labour. It is hard to believe that one of the two authors of the chapter on uterine stimulants and relaxants is a pharmacologist. The whole chapter reads like the essay of a student doomed to fail his exams. For example prostaglandin synthesis is apparently a closed book. Diazoxide is stated to be a *diuretic*, which *increases* insulin secretion! Ether, but not halothane, is stated to be a *volatile gas!* (Both are of course volatile liquids). Chapter 12 is called 'Obstetric analgesia and anesthesia', but sets out to describe first the physiological changes of pregnancy. It then goes on to give practical descriptions of anaesthetic techniques, which is surely inappropriate for this book. It is misleading in parts: for example halothane is said to produce analgesia, and thiopentone appears under the heading of inhalational anaesthetics. The bald statement 'The role of amniotic fluid in fetal pharmacology is unknown' would be forgivable if the authors then cited a clutch of references to show they realise how much had actually been written about it. The sentence 'The first principle of fetal resuscitation is to avoid it' sounds surprising, and is followed by a homily on care of the parturient which has little to do with drug use in pregnancy. The final chapter on the enhancement of fetal lung maturation (which logically should have preceded chapter 12) is clear in content, brief (thank goodness) and informative. My only criticism is it made no mention of the implications of ruptured membranes.

Drug Prescribing in Pregnancy, by Krauer, Krauer and Hytten, comprises three well-conceived chapters. The first, on general considerations and principles of drug prescribing, covers teratogenesis and epidemiology of drug use. It is utterly clear and succinct, and the extensive literature on the subject is given, thank heaven, in tabulated form. The second chapter is on the effects of pregnancy on drug handling, and describes the physiological changes of pregnancy and the theories of pharmacokinetics in this context. Reading this section I found myself saying 'what about the facts?'—but never fear, they all come in chapter 3. This contains an abundance of information on pharmacokinetics in pregnancy, and despite the excellent brevity of the book is quite remarkably comprehensive, thanks again to some excellently concocted tables. I have a few minor criticisms. In the section on uptake of general anaesthetics, not strictly germain to pregnancy, the authors needed the advice of an anaesthetist! In some confusion they find themselves stating, for instance, that ether and halothane are less lipid-soluble than nitrous oxide (they are actually about 40 and 100 times more so, respectively!). The reduced binding of phenytoin in pregnancy is forgotten in suggesting the therapeutic ranges are the same as for the non-pregnant. Vasculosyncytial membranes are said to have no known advantage, whereas the formula cited for placental transfer clearly shows the advantage of membrane thinness for diffusion of respiratory gases (or am I being too simplistic?). The word 'basic' is used erroneously to describe an *alkaline* solution. These are merely nit-picking. The book is excellently planned, beautifully written and emminently useful.

Felicity Reynolds

Perinatal Pathology Vol 15 in the series *Major Problems in Pathology*, Jonathan S. Wigglesworth. W. B. Saunders, London, 1984, 447 pages with figures and tables, £42.50

This book does not set out to provide a detailed and encyclopaedic account of perinatal pathology but is specifically aimed at the non-specialist pathologist who has to perform occasional perinatal autopsies. The first nine chapters are devoted to general topics such as perinatal infections, malformations and the causes and classification of perinatal death. There is a valuable chapter on the technique of the perinatal autopsy and a chapter devoted to the placenta in which the author defines eminently sensible indications for sending the placenta for pathological examination. The next 10 chapters are concerned with the pathology of the various systems whilst the final chapter considers the perennial problems of unexpected death in infancy. The author has managed to compress a good deal of information within the confines of what is, by current standards, a relatively small volume and has been clearly helped in this task by his ability to write lucid, simple, correct English. The illustrations are generally excellent and there is a comprehensive index. This book will obviously be of great value to those pathologists who venture infrequently into the field of perinatal pathology and it is highly probable that some pathologists who quite commonly perform perinatal autopsies would also benefit from a thorough reading of its contents. Trainees in pathology will find that this book contains all they need to know about perinatal pathology (i.e. more than their examiners) whilst I feel it will be an invaluable volume to perinatalogists and obstetricians: for these two latter groups there is not only a clear indication of the achievements of perinatal pathology but also of its limitations, for the pathologist cannot invariably provide a precise cause of perinatal death.

H. Fox

Birth Counts Statistics of Pregnancy and Childbirth Alison Macfarlane & Miranda Mugford. Her Majesty's Stationery Office, London, 1984, Volume 1 345 pages with figures and tables, £9.95, Volume 2 Tables, 324 pages, £19.95

'And he asked him, "What is thy name?" and he answered saying "My name is Legion: for we are many".' So too are the statistics of pregnancy and childbirth which are brought together in 'Birth Counts'. The book appears in two volumes. Volume one is a review of the very wide range of statistics about pregnancy, childbirth and new born babies collected by central and local government and the National Health Service in England, Wales, Scotland and Northern Ireland. In describing the available statistics the authors offer a critical appraisal of data and the way it is presented. The importance of this aspect will not be lost on anyone who has had to sit and be harrangued by a lecturer using statistics—like a drunken man uses a lampost, more for support than illumination. This is particularly true in the realm of international comparisons when, for example, the perinatal mortality position of England and Wales is unfavourably compared with other countries who use different definitions and classifications. As George Bernard Shaw said 'Even trained statisticians often fail to appreciate the extent to which statistics are vitiated by the unrecorded assumptions of their interpreters'. The authors, in the last chapter of the first book, make this point but also point to the value of official statistics properly used to help identify problems and their possible solutions. A valuable appendix to this volume gives comprehensive guidance on where to seek information on all relevant health statistics. Volume II contains 170 tables of data. The subjects covered range from geographical variations and social class differences in births and mortality, to regional variations in operative intervention in labour. The tables mostly refer to the last 10 years and are, perhaps, not quite as up to date as one would wish, in most cases stopping short at 1980 or 1981. Nevertheless, the tables themselves make fascinating reading and for the would be lecturer (*vide supra*!) provide material for endless slides. The authors are to be congratulated on putting together such a mine of information and providing the necessary explanations and interpretations for the non-statistician. The two volumes are sold separately but are really complimentary and by modern standards they are not expensive. Not every obstetrician and gynaecologist will want to have personal copies but all should have access to these valuable books, which should certainly be in every departmental library.

M. Brudenell

The Epidemiology of the Cerebral Palsies edited by Fiona Stanley & Eva Alberman. Blackwell Scientific Publications Ltd, Oxford, 1984. 188 pages with figures and tables. £12.50

This is an invaluable up-to-date review of the epidemiology and aeriology of cerebral palsy, edited by Professor Eva Alberman, of the London Hospital, and Fiona Stanley, of Western Australia—with their own massive contributions. Their contributors were Eva Blair of Western Australia, Bengt and Gudrun Hagberg of Sweden, John Kiely and Nigel Paneth of New York, Tom Ingram, Edmund Hey, Stephen Jarvis, Paul Polani and Jonathan Wigglesworth of UK. Subjects include classification and incidence of cerebral palsy, brain development and its modification by adverse influences, measurement of disability, risk factors—prenatal, perinatal and postnatal, and the difficulties of epidemiological and aetiological studies. The Editors remark that 'the study of the cerebral palsies presents epidemiologists with every possible pitfall'; but they provide an admirable review of the aetiological and associated factors, with special emphasis on the complicated multiple inter-relations between cerebral palsy and low birth weight, duration of gestation, intrauterine growth retardation, multiple pregnancy, relative infertility, haemorrhage or infections during pregnancy, social factors including maternal age, parity and poor antenatal attendance, breech presentation and other labour problems. They noted the greater incidence of congenital anomalies in cerebral palsy—and their association with complications of labour, such as breech presentation, prolapse of the cord or prolonged labour. Many of the so called risk factors may be subclinical and therefore difficult to identify, except perhaps by retrospective studies of affected children and controls. Minor cerebral malformation which may predispose to brain damage at birth may elude identification except at autopsy; and tests for intrauterine infections are not routinely made in cerebral palsy. The authors discuss the way in which the various known risk factors may predispose to brain damage at birth. They suspect that while the infant may successfully withstand one or two damaging factors at birth, multiple factors may result in brain damage. Other difficulties in epidemiological studies include terminology and classification (such confusing terms as dystonia, ataxic diplegia, double hemiplegia, 'mixed cases'), inaccuracy of definition of hypoxia, brain damage, fetal distress, etc., paucity of autopsy studies, the relatively low prevalence of cerebral palsy (e.g. 2/1000 live births) making prospective studies expensive and time-consuming, delayed diagnosis of cerebral palsy, inaccurate retrospective data, and lack of uniformity of records. This is an excellent study, for which the editors deserve every congratulation. The volume should certainly have its place on the book shelves of every obstetrical unit.

Ronald Illingworth

Colposcopy Cervical Pathology. Textbook and Atlas by Erich Burghardt. Georg Thieme Verlag, Stuttgart, 1984, 268 pages fully illustrated with 365 plates mostly in colour, DM198

Over the last decade colposcopy has assumed ever increasing importance in British gynaecological practice with the formation of a national society, the holding of a world congress and many training courses. The colposcope was invented by Hinselmann in 1925 and Erich Burghardt, his countryman, is an internationally recognized expert in the field. His textbook is the product of many years of experience. There can be no real substitute for multiple examinations in the recognition of colposcopic appearances but the coloured photographs in this atlas are quite magnificent. They provide the would-be colposcopist with a full range of appearances with which he or she can become familiar in the comfort of an armchair. The author is also a professor of pathology and a sound knowledge of the latter is necessary for a clear understanding of colposcopy. This is thoroughly described in the textbook accompanied by a wealth of photomicrographs. Definite differences do exist between British and Continental practice and the experienced individual will savour the discussion. Destructive techniques are rapidly becoming the mainstay of treatment of cervical intraepithelial neoplasia in this country. This is denigrated by the author who argues strongly for the traditional approach of cone biopsy. Microinvasive carcinoma of the cervix is dealt with in detail and here Burghardt's classification is being adopted with some modification by Britain and the International Federation for Obstetrics and Gynaecology. This book provides valuable reading for anyone with an interest in colposcopy whether novice or expert.

Ian D. Duncan

Books received, some of which will be reviewed at a later date

Progress in Obstetrics and Gynaecology Volume 4 edited by John Studd. Churchill Livingstone, Edinburgh, 1984, 394 pages illustrated, £15.00

New Surgical Trends and Intergrated Therapies in Gynaecologic Oncology: Cervical, Ovarian, Breast Cancer Proceedings of the Third International Meeting of Gynaecologic Oncology, edited by A. Onnis. S.O.G. srl Padua (Italy) Montreal (Canada), 1983, $60

Viral Hepatitis: A Problem in a Hospital Practice edited by Rosalinde Hurley. S.O.G. srl Padua (Italy) Montreal (Canada), 1984, 78 pages, illustrated, $10

Disease and Fertility by Joseph A. McFalls Jr. & Marguerite Harvey McFalls. Academic Press Inc, Orlando, Florida, 1984, 593 pages, illustrated, $69.50, £49.00

A Manual of Natural Family Planning by Anna M. Flynn & Melissa Brooks. George Allen & Unwin, London, 1984, 134 pages with figures and tables, £8.95

The Gift of A Child by Robert & Elizabeth Snowden. George Allen & Unwin, London, 1984, 118 pages, paperback £4.95, hardback £8.95

Cell Culture Methods for Molecular and Cell Biology. Volume 2 Methods for Serum-Free Culture of Cells of the Endocrine System edited by David W. Barnes, David A. Sirbasku & Gordon H. Sato. Alan R. Liss Inc, New York, 1984, 272 pages with figures and tables, £30.00

Coping with Childlessness by Diane & Peter Houghton, George Allen & Unwin, London, 1984, 176 pages, £8.95

Clinical Gynecologic Oncology Second Edition by Philip J. Disaia & William T. Creasman. The C.V. Mosby Company, St Louis, 1984, 580 pages, fully illustrated, £38.00

Reproduction: The New Frontier in Occupational and Environmental Health Research. Progress in Clinical and Biological Research Vol 160 edited by James E. Lockey, Grace K. Lemasters & William R. Keye Jr. Alan R. Liss Inc, New York, 1984, 606 pages with figures and tables, £52.00

Key Facts in Embryology by M. W. Rana. Churchill Livingstone, Edinburgh, 1984, 245 pages with figures and tables, £14.75

Osteoporosis Volumes 1 & 2 Proceedings of Copenhagen International Symposium on Osteoporosis June 1984 edited by C. Christiansen, C. D. Arnaud, B. E. C. Nordin, A. M. Parfitt, W. A. Peck & B. L. Riggs. Published by Dept of Clinical Chemistry, Glostrup Hospital, University of Copenhagen, 2600 Glostrup, Denmark, DK 700

Female Puberty and its Abnormalities Vol. 9 Current Reviews in Obstetrics and Gynaecology by Sir John Dewhurst. Churchill Livingstone, Edinburgh, 1984, 204 pages, illustrated, £11.00

Current Concepts in Surfactant Research Vol. 18 in the series Progress in Respiration Research edited by P. von Wichert. Karger, Basel, 1984, 310 pages illustrated SwFr 247, DM 296, US$148.00

Perinatal Epidemiology by M. B. Bracken. Oxford University Press, Oxford 1984, 550 pages with figures and tables, £40.00

Pregnancy, Diabetes and Birth. A management guide by Dorothy Reycroft. Hollingsworth. Williams & Wilkins, London, 1984, 166 pages illustrated, £32.00

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Pregnancy and its management W. A. W. Walters (Melbourne, Australia)

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Human conception in vitro: new opportunities in medicine and research—R. G Edwards (Cambridge, UK)

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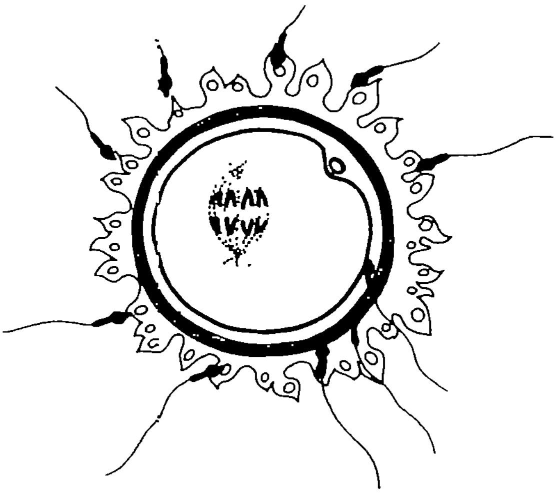

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Two copies of the manuscript and illustrations should be sent. Manuscripts should be typed double spaced on one side of the paper, with wide margins The names of author(s) and their appointment(s) and addresses at the time of preparation of the manuscript should appear at the head of the paper; present addresses, if different, will be given as a footnote.

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Reports of original work should usually be arranged in the conventional order of summary, introduction, methods, results, discussion, acknowledgments and references, with suitable headings for each part. Two further sub-divisions, with appropriately less significant headings, can be used; the third order heading runs on with text at a paragraph opening. Results may be presented in the text, in tables and/or figures, but the text should, in general, comment on rather than repeat information in tables

The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s), brief communications require no summary.

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin Both are numbered with arabic numerals Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction.

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Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs. Original X-ray films should not be sent—glossy prints must be submitted

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

Typewritten lettering should not be used on illustrations and explanations should appear in the legend not on the figure itself.

The identity of patients in illustrations should be concealed by masking the face or eyes; or written permission for publication from the patient or the parent or guardian must be supplied.

Units and abbreviations

Measurements should be expressed in SI units with the exception of haemoglobin (g/dl) and blood pressure (mmHg). If the original observations were recorded in other units this should be stated, together with the appropriate conversion factors Standard abbreviations, without punctuation, are used *Units, Symbols and Abbreviations* (1977) published by the Royal Society of Medicine provides a useful guide. Abbreviations are used sparingly and only if a lengthy name or expression is repeated frequently throughout the manuscript. Words must appear in full on first appearance in both summary and text, followed by the abbreviation in parenthesis.

Drugs are described by their official names but trade names should be indicated in brackets the first time a drug is quoted in the main text.

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Authors should describe the plan of their investigation indicating the number of experimental units (e.g. subjects, blood samples). For repeated observations their numbers and timing should be specified. Control subjects should be described as completely as the experimental subjects.

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British Journal of Obstetrics and Gynaecology
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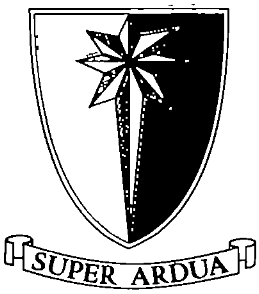
Edited by Frank E. Hytten



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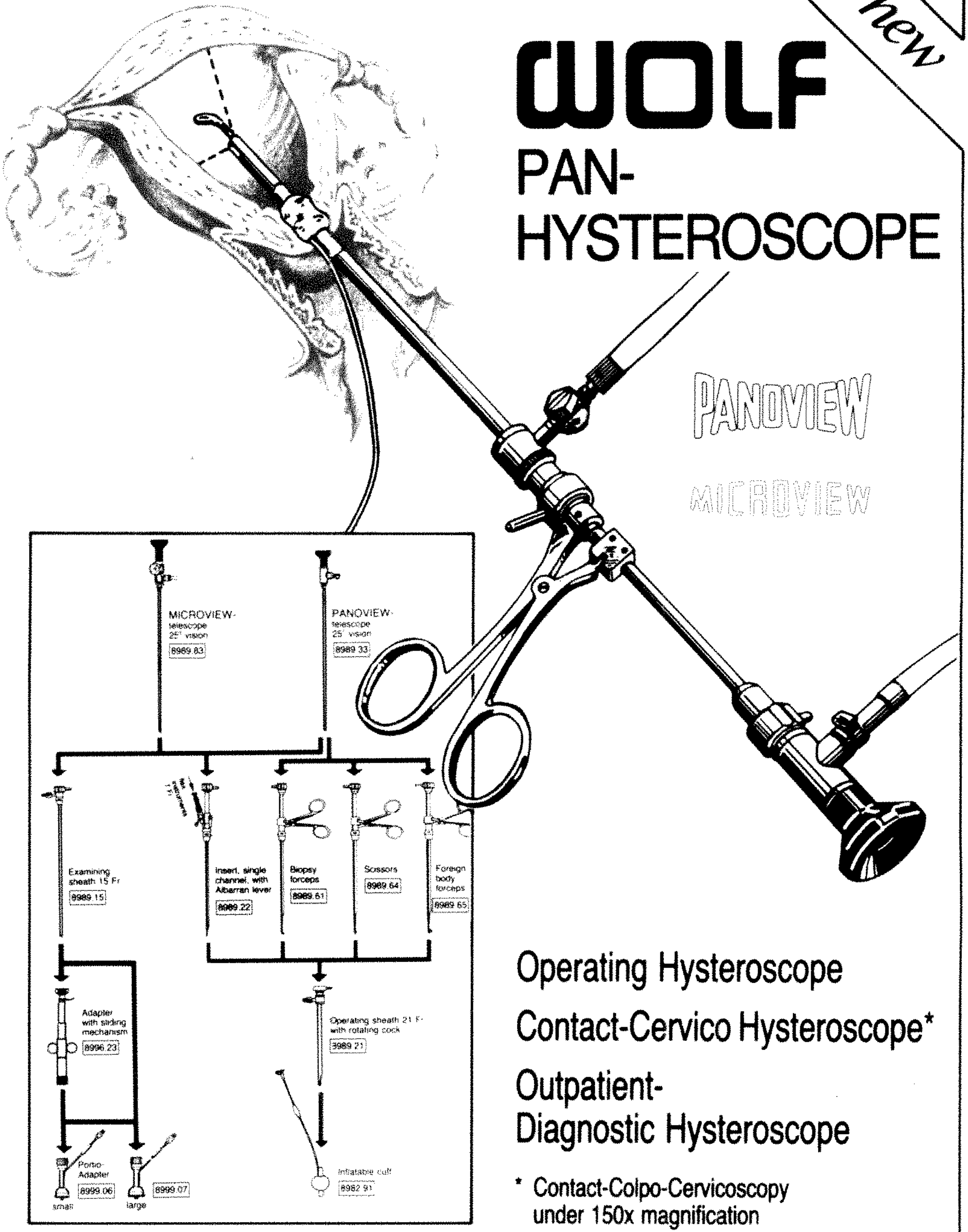

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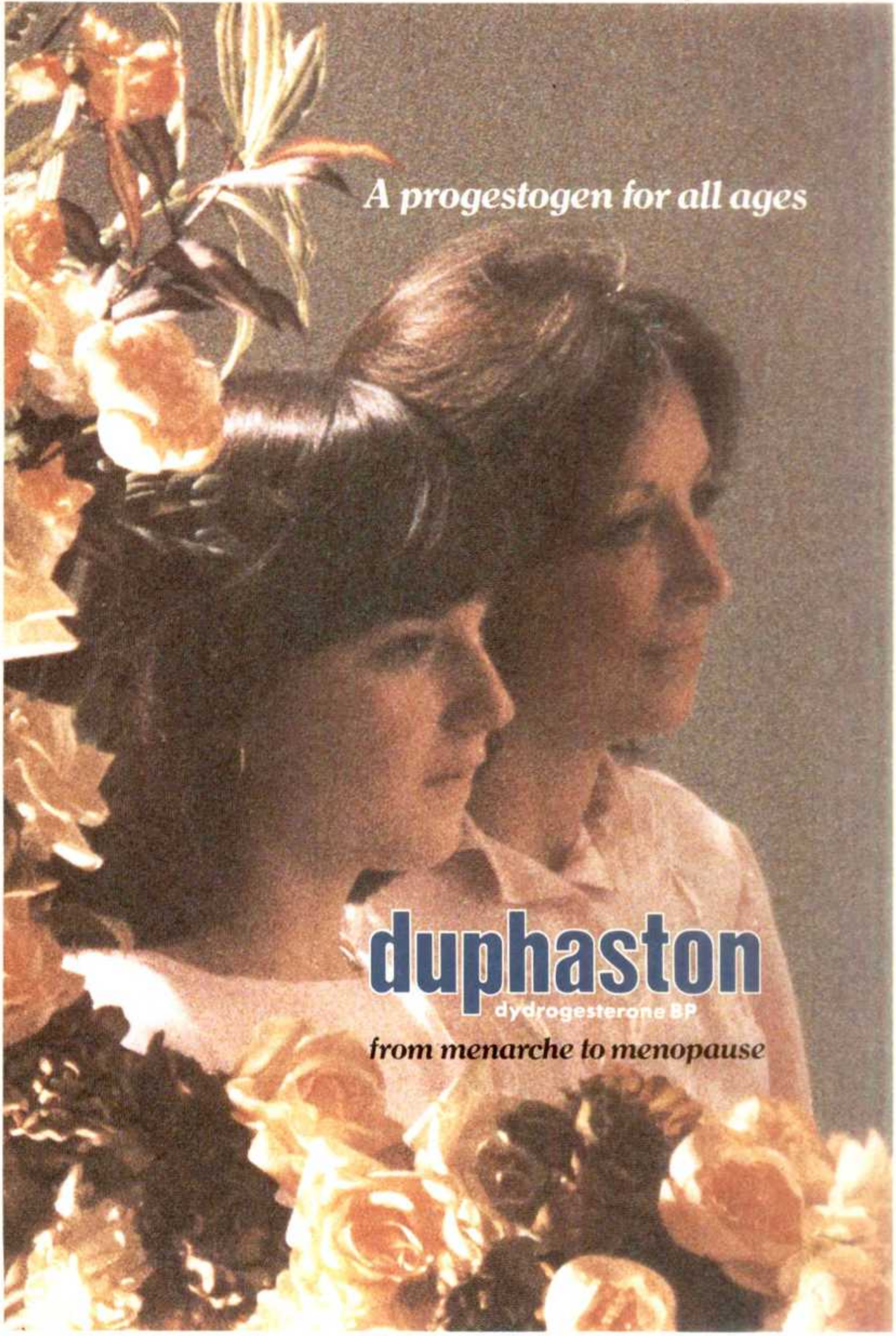

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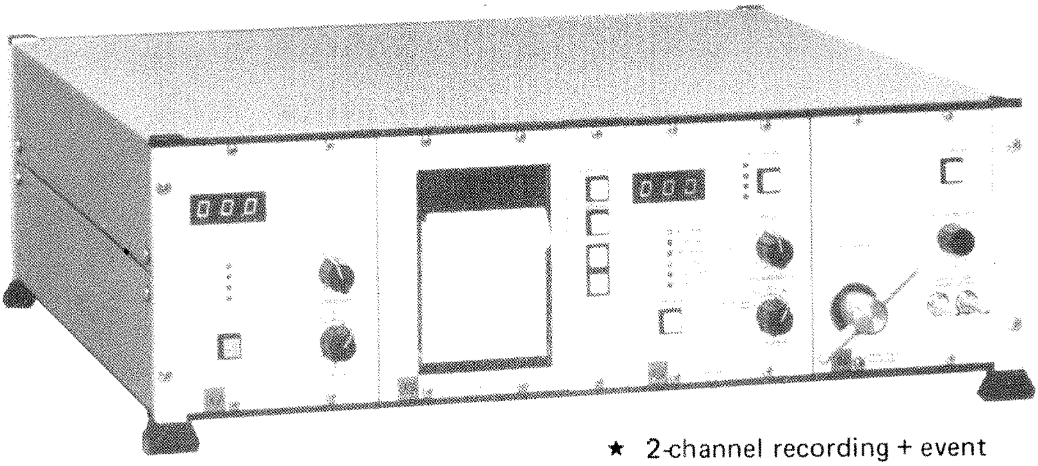

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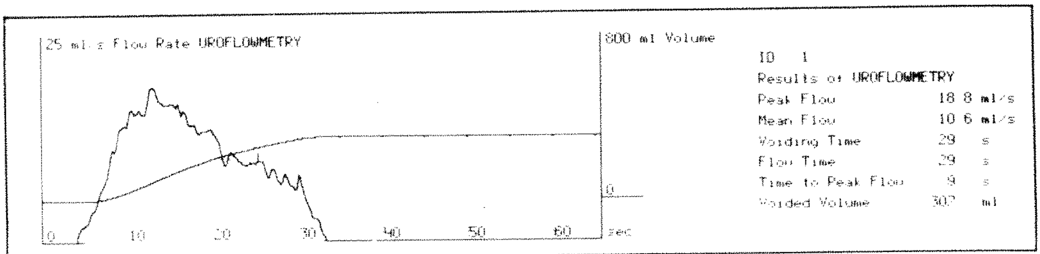

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COMMENTARY

Two wise men

The problems experienced by one generation may not be the same as those of its predecessors or successors. This is certainly true in the field of perinatal medicine. At the time when two of the contributors to this issue of the Journal, Sir Dugald Baird and Professor Illingworth, qualified in medicine (in 1922 and 1934 respectively), maternal mortality was causing such concern that government enquiries were being undertaken (Departmental Committee on Maternal Mortality and Morbidity 1932), stillbirth rates were high (40·8/1000 total births) (Macfarlane & Mugford 1984) and birth trauma was a serious problem. Holland (1922) found in his study *The Causation of Foetal Death* that 52% of stillbirths were the result of birth trauma. In 1948 in Aberdeen, as Sir Dugald Baird points out (page 115), birth trauma still accounted for 20% of all perinatal deaths, compared with only 3% of such deaths in Scotland in 1981.

As death from mechanical problems during labour and delivery is now such a rare event, why has there been so much concern about birth injury in recent times? Litigation may be the reason. A leading article in the *Lancet* (1984) pointed out that defensive obstetrics was not much talked about until the late 1970s. At that time, 'repeated and contradictory judgements' were made in the Whitehouse *vs* Jordan case. Shortly afterwards Professor Illingworth published 'Why blame the obstetrician?' (Illingworth 1979). He wrote, 'It is essential to look behind obvious difficulties in labour, such as abnormal presentation or anoxia, to the underlying causes, which are often genetic or social or concern other prenatal factors'. Today (on page 122) he develops this theme further. He points out that it is irrational to attribute a child's so called 'brain damage' to labour or delivery without considering other factors such as maternal health before and during pregnancy, difficulties during labour and delivery, and their interaction. He also draws our attention to the fact that children who have suffered a traumatic delivery frequently develop normally and that delivery by caesarean section is no guarantee against brain damage.

Recent research supports these views. In a case-control study from Oxford, Niswander *et al.* (1984) have reviewed adverse outcomes of pregnancy and the quality of obstetric care. They concluded that fetal deaths ascribed to asphyxia and trauma, and very early neonatal seizures in babies born at term are valid indicators of obstetric care; that severe intrapartum fetal distress must be acted upon promptly; but 'individual cases of cerebral palsy and other forms of adverse pregnancy outcome are in most cases unlikely to have been caused by suboptimal obstetric care as defined in this study'.

Sir Dugald Baird discusses other problems in obstetrics. His hypothesis is that certain complications are predetermined, because of environmental problems in the past. Thus the incidence of anencephaly varies, rising, it is suggested, in the daughters of women who were themselves conceived in times of hardship. The same may be true for low birthweight. By linking data about mothers who had low-birthweight infants in the early 1970s in Aberdeen to those of the grandmothers' pregnancies in the 1950s and differentiating low birthweight into two types (obstetric and unexplained) Sir Dugald argues that unexplained low birthweight may in many instances be predetermined. The findings from his small series are certainly interesting and we look forward to more detailed studies from the Aberdeen Maternity Data Bank which has been collecting information about all pregnancies since 1951 and is now about to present intergenerational data.

The two wise men are warning us from their different standpoints that problems will occur that cannot be prevented by more active intervention.

Professor Illingworth calls for research into various methods of management of the perinatal period—'What good may it do . . .?' 'What harm may it do?' 'What harm may result from not doing it?' Sir Dugald calls for more attention to be paid to the emotional needs of the mother not only during the actual pregnancy and labour but also in relation to wider problems. We must heed the warnings of these two wise men.

Gillian McIlwaine

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Changing problems and priorities in obstetrics

SIR DUGALD BAIRD *Manor House, Boswall Road, Edinburgh*

Summary. National perinatal mortality data suggest that the root causes of many deaths may lie in the environmental circumstances in which the mother grew up. Aberdeen primigravidae under the age of 20 years who gave birth to a baby with a birthweight of <2500 g between 1968 and 1972 were divided into those where there was an associated obstetric complication and those where the cause of the low birthweight infant was 'unexplained'. The 'unexplained' group were more often smaller, underweight, cigarette smokers, and from relatively large families in the lower socioeconomic classes. Investigations of case records and by interview revealed that the mothers of these primigravidae were similarly disadvantaged and it is argued that further improvement in perinatal health and mortality will depend on the elimination of this continuity of social disadvantage.

Reproductive efficiency is related to the mother's health and physique, which in turn is related to the quality of the environment in which she grew up. In the first year of life specific illnesses may lead to death or serious morbidity, but the relation of environmental circumstances to the causation of perinatal deaths may only become clear some 20 years later. It is, of course, likely that the improved diets of pregnant women and full employment in the 1940s was, to a large extent, responsible for the rapid fall in the perinatal mortality rate in these years. However, expert opinion was that by 1948 there was relatively little scope for further reduction in the perinatal mortality rate by improvements in the mother's food intake during pregnancy.

In Scotland, unlike England and Wales, the perinatal mortality rate fell by 15% between 1948 and 1957. In the city of Aberdeen it fell by 35% in the same period because of a number of very favourable happenings, including an immediate increase in the number of obstetric hospital beds, an increase in the number of National Health Service consultants and university lecturers with consultant status, and a great increase in research facilities. The fall in the perinatal mortality rate ceased during the years 1958–1962 largely because 15% of Aberdeen mothers, mostly women of high parity from social classes IV and V, preferred to book for a home birth. Many of these women were admitted as emergencies and, not surprisingly, perinatal death rates were high in this group. These women were also the last of the cohort who had been born during the years of the deep depression in the late 1920s and early 1930s and had, as a result, high perinatal mortality especially from low birthweight and central nervous system malformations in each of their pregnancies.

From 1960 the standard of obstetrics and the perinatal mortality rate improved steadily. It was generally agreed that children born during and after the war were taller, healthier and better cared for than those of the previous generation. What would happen when these children started childbearing in the late 1960s? In Scotland, for first pregnancies in social classes IV and V the rapid fall in the perinatal mortality rate was suddenly arrested from 1968 to 1974 but this did not happen in social classes I and II. Fig. 1 shows that in social classes IV and V the stillbirth rate in the 15–19 age group fell rapidly from 1962 to 1967, but in the following 10 years it was stationary and in 1973–1976 it actually rose. In the 25–29 age group the interruption in the fall in the rate lasted only 3 years. In the 20–24 age

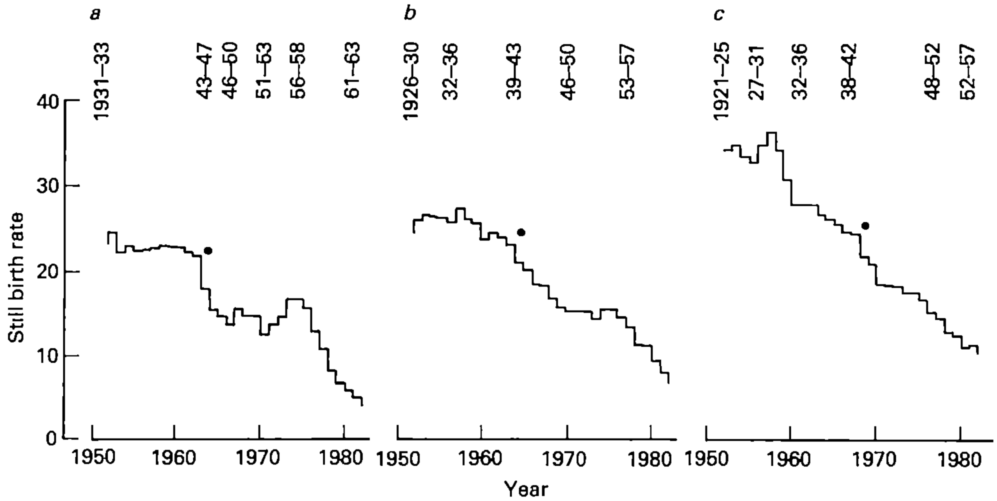

Fig. 1. Stillbirth rate in primigravidae in social classes IV and V by age and year of birth, Scotland 1950–1981 (3-year moving average). (*a*) 15–19, (*b*) 20–24, (*c*) 25–29.

group the changes were intermediate between those in the other two age groups. In all three age groups the fall in the stillbirth rate began in those mothers born since the beginning of the war. It is possible therefore that the food rationing policy not only resulted in a fall in the stillbirth rate in those years but may also have laid the foundations for improved reproductive efficiency of the young mothers of the late 1960s. But this does not explain the sudden deterioration, especially in the high-risk 15–19 age group.

From Aberdeen data it could be shown that in primigravidae in the late 1960s and early 1970s the perinatal mortality rate from low birthweight and central nervous system malformations rose sharply in the 15–19 age group which more than neutralized any fall in the rate from other causes (Baird 1974*a*, *b*).

Anencephaly has proved to be a very useful tool for studying, on a national scale, the relation between socioeconomic conditions and reproductive efficiency (Baird 1980). Fig. 2 shows that the stillbirth rate from anencephaly in the 15–19 age group rose to over 4 per 1000 in the late 1940s and early 1950s at a time when other causes of stillbirth were falling and again in the early 1970s. The introduction of abortion for central nervous system malformations from 1974 onwards may just have forestalled a rise in the 20–24 age group from 1975; the stillbirth rate from anencephaly would have remained high after 1974 if no abortions had been performed. In the late 1960s when the stillbirth rate in the 15–19 age group was falling rapidly there was no reason to believe that the quality of the diet in these pregnant women deteriorated suddenly. The rise in the rate resembled very closely that which occurred 20 years earlier in women who were born during the worst of the depression in the late 1920s and early 1930s. There is also good evidence that the stillbirth rate from central nervous system malformations rose sharply in the 1920s in women born during the severe depression which occurred at the end of last century. Thus, in the vulnerable social classes at least, three successive generations of mothers had high stillbirth rates from central nervous system malformations and in all probability from low birthweight. The rise in the death rate from these causes from 1968 occurred against the background of improved health and physique of the young adults of today. There is, of course, a limit to what can be achieved in one generation in improving the level of health and physique, and there remains an obvious social class gradient in the mean height of young adults in Britain, in contrast to Sweden where there is no longer a social or geographical gradient in the height of young adults (Lindgren 1976).

There are also limits to what can be done in one generation in animals, where experiments can be very effectively controlled. Stewart *et al.* (1980) showed that a diet deficient in protein

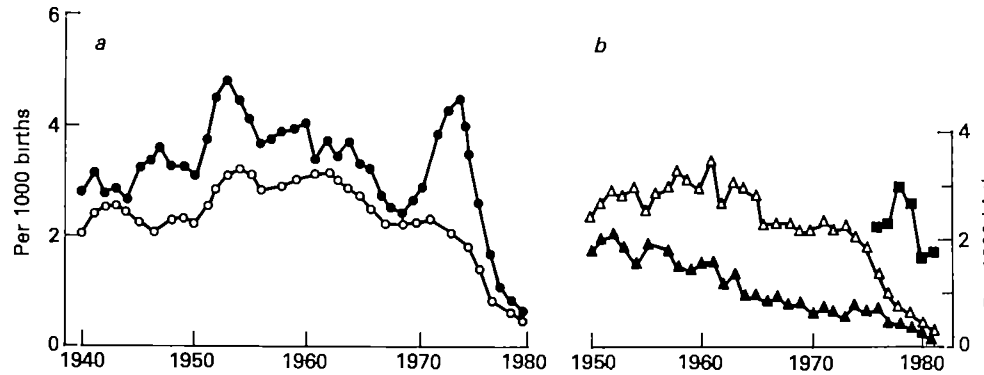

Fig. 2. (*a*) Stillbirth rate from anencephaly in age groups: 15–19 (●) and 20–24 (○), Scotland. (*b*) Stillbirth rate in all age groups from anencephaly (△), all other CNS malformations (▲) and all CNS malformations between 1976 and 1981 if therapeutic abortions had not been done in these years (■).

energy induced low birthweight and high infant mortality rates in colonies of rats where the females were 30% below the weight of control groups of well-fed rats. With a return to adequate feeding in the colony at least three generations were required to eliminate the damage done to reproductive efficiency.

During the years 1968 to 1972, 1117 primigravidae under the age of 20 years, resident in the city of Aberdeen, gave birth to a baby in the Aberdeen Maternity Hospital. In 108 cases the babies weighed <2500 g (7·2% in social classes I–III, and 14% in social classes IV and V). In 59 patients the low birthweight was unexplained clinically, whereas an obstetric complication was present in the other 49, namely, pre-eclampsia (22), antepartum haemorrhage (10), maternal disease (11) and fetal deformity (6).

Thirty-nine of the 59 mothers with clinically 'unexplained' low-birthweight babies came from social classes IV and V and 31 (52%) were light for their height (Table 1). Of the 49 women who had an obstetric cause for the low birthweight, 18 came from social classes IV and V and only 9 (18%) were light for their height. When height alone is considered, 30% of the women in classes I–III were short in stature (<61 inches, 155 cm) compared with 44% in classes IV and V. Thus, of all the women who had low-birthweight babies 38% were very short in stature and 53% came from social classes IV and V. Of the group of women with unexplained low birthweight, two-thirds came from social classes IV and V, and half of them were very short in stature and underweight, all very strong evidence that they had been reared in depressed socioeconomic circumstances.

An attempt was made to interview the 'index' mothers and their own mothers (the 'grandmothers'). This included home visits to assess the quality of the home environment and the mother's competence and personality. Details of social and obstetric histories of 'index' mothers, their sisters and their mothers (the grandmothers) were obtained. Unfortunately data were available for the grandmothers in only 28 of the 49 women where an obstetric factor was responsible and in 46 of the 59 women where the low birthweight was unexplained. In some cases obstetric details for the grandmothers were poorly recorded, especially when the birth took place at home; some of them were considerably older and multiparous at the time of the birth of the index mother. In view of this, detailed statistical analysis of the data has not been attempted but it has been possible to reach convincing conclusions.

In the obstetric-cause group individual grandmothers and their daughters (the index mothers) were very alike in height (most being between 61

Table 1. Social class and body build in mothers of low-birthweight infants born in Aberdeen 1968–1972

	Cause of low birthweight					
	Unexplained			Obstetric factors		
		Social class			Social class	
Body build	Total	I–III	IV–V	Total	I–III	IV–V
Heavy	6	2	4	12	9	3
Standard	22	8	14	28	16	12
Light	31	10	21	9	6	3
Total	59	20	39	49	31	18

Table 2. Body build, height, weight gain of index mothers and maternal grandmothers of low-birthweight infants born in Aberdeen 1968–1972

	Cause of low birthweight			
	Unexplained		Obstetric factors	
	Index mother	Grandmother	Index mother	Grandmother
Body build				
Heavy	5 (11)	11 (24)	4 (14)	8 (29)
Standard	18 (39)	14 (30)	18 (64)	9 (32)
Light	13 (28)	13 (28)	6 (21)	3 (11)
Not known	10	8	0	8
Height				
Tall	4 (9)	5 (11)	9 (32)	4 (14)
Medium	19 (41)	23 (50)	11 (39)	12 (43)
Small	23 (50)	16 (35)	8 (29)	6 (21)
Not known		2	0	6
Weight gain 20–30 weeks				
<5 lbs	9 (20)	4 (9)	3 (11)	3 (11)
6–10 lbs	16 (35)	16 (35)	7 (25)	5 (18)
>10 lbs	10 (22)	13 (28)	16 (57)	12 (43)
Not known	11	13	2	8

Results are numbers of women, with percentages in parentheses.

and 63 inches; 155–160 cm) and in body build. In 22 of the cases, where pre-eclampsia was the cause of the low birthweight, approximately half of the index mothers and grandmothers gained >10 pounds (4·5 kg) in weight in the 20–30 week period. Ten grandmothers had hypertension in the pregnancy which resulted in the birth of an index mother, and eight of them had hypertension in other pregnancies. In the unexplained-cause group the only common feature which stands out is short stature. Conclusions about weight gain in pregnancy and body build were not possible in some cases because of differences in age and parity. One-third of the index mothers and grandmothers were considerably underweight and one-third of index mothers gained less than 6 pounds (2·7 kg) in the 20–30 week period (Table 2).

In an attempt to understand more about maternal factors, in addition to the official social classification likely to influence obstetric outcome, a careful physical examination and interview was undertaken in approximately 2000 primigravidae attending the antenatal outpatient department of the Aberdeen Maternity Hospital during the years 1950–1952. Their general health and physique and competence was assessed and allocated to one of four grades. In due course it was found that the incidence of low birthweight (⩽2500 g) rose steadily from just <4% in those assessed as being in excellent health (group A) to 16% in those assessed as being in very poor health (group D). This relation could be seen to some extent inside each age, height and social class group. The highest incidence of low birthweight occurred in short women under the age of 20 and the lowest in tall women in the 25–29 age group. There was a close agreement between the level of competence and that of physical health. The outcome of pregnancy was best in women of standard weight for height who gained approximately 1 pound (454 g) per week in the 20–36 week period. Heavy women, especially those who gained more than 1 pound weekly, tended to have heavier babies or to develop pre-eclampsia. Light women who gained small amounts had an increased incidence of low-birthweight babies either as a result of short gestation or retarded intrauterine growth.

It transpired that 34 of the 108 grandmothers in the present study had been assessed, and the grade in 1950–1952 was recorded in their case records. Of 17 grandmothers whose daughters had a low-birthweight baby for an obstetric reason, two were assessed as A and three as D. In 17 cases where the daughter had an 'unexplained' low-birthweight baby none of the grandmothers was assessed as belonging to group A but 10 were assessed as D. These early assessments of the grandmothers as primigavidae are in line with subsequent happenings; in the obstetric-cause group most were born between 1918 and 1926 with an even distribution over the years, whereas in the unexplained-cause group most were born between 1926 and 1933, with a concentration between 1930 and 1932—the years when the depression was at its worst. Grandmothers in the obstetric-cause group tended to have small families and came themselves from small stable families, as did their husbands; the only disturbing feature, where pre-eclampsia was the factor, was the frequency of arterial disease in the family background of husband or wife.

In the unexplained-cause group the situation was sometimes very different. The index mothers tended to come from large families, as did their husbands and the grandmothers. Unemployment and broken homes were not infrequent and home visits sometimes revealed slum conditions and neglected children. The family background of the index mother and her husband tended to be similar. Smoking habits were known in 74 of the 108 index mothers. In social classes I–IIIb, 11 out of 25 women smoked, usually less than 10 cigarettes daily. In classes IIIc–V, 41 out of 49 women smoked, 25 of these women came from social class V and 23 of them said they smoked 20 or more cigarettes daily.

In a survey of 8088 children born in Aberdeen in the years 1952–1954, 104 were assessed as mentally subnormal (Birch *et al.* 1970). A careful neurological examination was made in 91 of these children and 44 were found to have evidence of neurological damage, two-thirds of them having I.Q. scores <60. In this group there was relatively little social class difference in incidence. In the remaining 47, where no neurological evidence of damage was detected, 37 had scores of >60 and all but one of them came from social classes IIIc–V. Families were very large in this group and the mean I.Q. score of 115 siblings was 80. Seventeen in the 36 mothers of these children were <61 inches in height and 18 of them came from very large families.

Today, more than ever before, able children move up the social scale due to a large extent to careful planning by parents. For example, in Aberdeen in social class III (manual) the mean I.Q. score in first children of mothers aged ⩾35 years was 118 compared with 103 in families where the mother was <20 years of age. In fifth or later children the mean score was 103 when mothers were ⩾35 years of age and only 93 when the mother was <25 years of age. The relations between maternal age, family size and the infant mortality rate were exactly the opposite, the lowest death rate being in firstborn children to mothers over the age of 35. While the husband's occupation has proved to be a valuable tool in large-scale epidemiological research, the great human variations inside one official social class, as demonstrated above, is a reminder of the need for more refined methods of analysis in the elucidation of many problems.

A striking feature in Scotland today has been the rapid decrease in the number of births in social classes IV and V. The total in these classes fell from 30 605 in 1960 to 13 011 in 1982, compared with a small rise in classes I and II from 13 335 to 15 128 during the same period. In social classes I and II since 1960 there has been a slight increase in numbers in first and second pregnancies and a slight fall in numbers in the other parity groups. In classes IV and V numbers have fallen in all parity groups but most dramatically in fifth and later births since 1965. In 1960–1964, 16% of all births and 21% of all perinatal deaths in Scotland were in fifth or later pregnancies compared with 3·3% of births and 5% of all deaths in 1982. Sterilization has played an important part in this change. For example, in Aberdeen in 1951–1952 nearly 40% of sterilizations were done in women who had had five or more children, while in 1975–1976, 55% were done in women who had only two children and only 1% in women who had five or more children. This radical decrease in family size will lead to many fewer children being reared in poor socioeconomic circumstances and in overcrowded homes.

The reduction in family size is even more important today in a society where mechanization has reduced the number of jobs. A rise in the birth rate which lasted from 1957 to 1970 reached its peak in 1964 in which year the number of births in England and Wales was approximately 900 000. That was 200 000 more births than the number in 1957, which was sufficient for replacement. These children reached 16 years of age in 1980 and must therefore make the serious unemployment situation very much worse. Between 1973 and 1982 the net reproduction rate fell from 1·0 to 0 82.

In 1982 the perinatal mortality rate in England, Wales and in Scotland was just over 11 per 1000, but the low-birthweight baby continues to be the biggest single problem in obstetrics. In Scotland, McIlwaine *et al.* (1984) have shown that only 3% of all perinatal deaths in 1981 were from birth trauma, compared with a rate of 20% found in Aberdeen in 1948. The incidence and death rate from malformations not involving the central nervous system has remained stationary for many years and prevention awaits advances in genetic engineering. Excluding all malformations, 63% of all the remaining deaths in 1981 were in babies weighing <2500 g, 42% weighing <1500 g. Sixty-two per cent of these low-birthweight babies were in the 'unexplained' category. Aberdeen data show that such deaths occur typically in primigravidae under the age of 20 who are short in stature and underweight for their height. The perinatal mortality rate has fallen by more than 50% since 1974 but some of this improvement has been due to termination of pregnancy for central nervous system malformations. It is not possible to predict whether or not a rise in the incidence of low birthweight and central nervous system malformations will occur again in the late 1980s and early 1990s.

A change in sexual mores started in the late 1950s in young professional women in London and the South and spread slowly north and down the social scale. But in the absence of efficient contraception, unplanned pregnancies increased rapidly, which no doubt was partly why the Abortion Bill passed successfully through Parliament and abortion is now accepted as a necessary 'back stop' for failed contraception. In the city of Aberdeen, although contraception has been readily available for many years, 35% of all first pregnancies in 1971 were in young women under the age of 20, compared with 25% in 1961. Of these pregnancies 20% were terminated, 23% of babies were born outside marriage and only 12% of conceptions occurred after marriage. In the 25–29 age group, 85% of conceptions occurred after marriage, 30% after $\geqslant 3$ years of marriage. These two groups therefore seemed to be living in different worlds.

Women today are, on average, more enlightened on medical matters than ever before and less likely to run risks to their life, health and children. Consequently they must be aware of the vital part played by hospitalization and advances in knowledge and their practical application in making childbearing safer than ever before.

It is clear that today more time and attention must be paid to the emotional needs of the mother, not only during the actual pregnancy and labour but also in relation to wider problems. For example, the possible relation between the greatly reduced time involved in the reproductive process and possible effects on other organs and functions. For those who also wish to continue a career outside the home there can be great emotional stress.

The number of people with the combination of intelligence, ability, personality, vigour, common sense and sense of humour necessary to 'get to the top' and make a success of it is limited. Society cannot therefore afford to neglect 50% of such people because they happen to be women. Nor indeed can it afford to do without the able children they might produce.

It took 50 years for the Governments of this country to take some responsibility for the provision of a contraceptive service. Let us hope that it does not take as long to create a better society in which men and women have equal status.

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A paediatrician asks—why is it called birth injury?

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Summary. It is irrational to ascribe a child's so called 'brain damage' to labour or delivery without considering other factors. 'Brain damage' occurs without difficult labour or perinatal hypoxia and caesarean section is no guarantee against it. Severe difficulties in delivery and severe hypoxia at birth are in the great majority not followed by evidence of 'brain damage'. In the maternal history there is a significantly greater incidence of relative infertility, and of pregnancies associated with low birthweight or intrauterine growth retardation, postmaturity, antepartum haemorrhage, pre-eclampsia or infections. There are often genetic factors, more congenital anomalies and pathological evidence of underlying abnormality. There is an interaction of numerous factors, prenatal, perinatal and postnatal and it is simplistic to ascribe 'brain damage' to single factors, such as breech delivery or hypoxia at birth, without considering the antecedent causes of those factors.

I am constantly impressed by the readiness with which doctors accept the diagnosis of brain damage at birth. This article is written, with no obstetrical or neuropathological expertise, by a paediatrician attempting to summarize in a logical manner part of the vast literature, the difficulties in its interpretation, and the need for research.

The paper will discuss predominantly cerebral palsy, which is commonly ascribed to brain damage at birth, but will include mental subnormality when there are no known causes such as metabolic disease, hydrocephalus, chromosomal or other syndromes.

Cerebral palsy or mental subnormality with no known prenatal or perinatal factors

Numerous papers have examined the incidence of cerebral palsy or mental subnormality despite normal pregnancy and labour, and the absence of known hypoxia at any stage. A common difficulty in interpreting these papers is the absence of comparative information on the pregnancies which were not followed by the finding of 'brain damage'.

Normal delivery had occurred in 28% of the 400 cases of cerebral palsy described by Asher & Schonell (1950), in 59% of the 63 reported by Andersen (1957) and in 50% of the 142 reported by Holm (1982). It is notable that even in spastic hemiplegia, in which one might expect a higher incidence of 'birth injury', of a total of 442 cases described in three papers (Asher & Schonell 1950; Ingram 1964; Hagberg *et al.* 1976), delivery was 'normal' in 109 (25%).

The absence of known hypoxia at any stage was noted in many papers. Churchill (1970), in a study of 45 preterm infants with cerebral palsy, found that their mean Apgar score was no less than that in non-spastic preterm infants of the same gestational age. In the American collaborative study on cerebral palsy and mental retardation, Nelson & Ellenberg (1981) investigating infants with cerebral palsy found that Apgar scores of $\geqslant 7$ had been present in 55% at 1 min and in 73% at 5 min.

Paine (1968) in his study of 1100 children with cerebral palsy in Boston, examined the whole of pregnancy for risk factors, and could find 'no plausible etiologic factor' in around 30%. Durkin *et al.* (1976), in their study of 281 cases of severe cerebral palsy and mental subnormality, found that a third had a 'completely clean history', a third had 'minor problems not usually associated

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with a bad outcome' and a third had complications serious enough to account for the handicap.

It would seem less likely that birth injury would explain the occurrence of mental subnormality in the absence of cerebral palsy, yet many doctors are ready to ascribe it to birth injury. The product of four representative reports (Fairweather & Illsley 1960; Roberts 1966; Drillien 1968; Hunter *et al.* 1980) from Britain and Canada, analysing 1392 cases of mental subnormality without cerebral palsy, indicated that 840 (60%) were of unknown aetiology—with no evidence of pregnancy or perinatal factors. But Fairweather & Illsley (1960) in their study of 66 mentally subnormal persons in Aberdeen, following the work of Dugald Baird, noted the high frequency of marital and occupational instability in the parents, low parental intelligence, poor social conditions and high fertility.

It has become a widespread practice to claim that if only a caesarean section had been performed, brain damage would have been avoided. This may be correct in some cases; but it ignores the fact that caesarean section increases the maternal morbidity and mortality and that the child's Apgar score is likely to be lower than it is after vaginal delivery. Perhaps partly because of circumstances leading to caesarean section, the procedure is certainly no guarantee against cerebral palsy. For instance, Steer & Bonney (1962) found that 14 of their 276 children with cerebral palsy had been born by caesarean section; and Davies & Tizard (1975) in a controlled study showed that in low-birthweight babies, when gestational age and birthweight were equated, caesarean section did not alter the incidence of spastic diplegia.

Significance of prenatal factors

It is difficult to assess the incidence of prenatal factors for 'brain damage', because they are so numerous, and not all have been taken into consideration. Estimates often depend on the exclusion of known perinatal problems such as difficult delivery or hypoxia.

Typical values given for the incidence of solely prenatal factors in cerebral palsy are those of O'Reilly & Walentynowicz (1981) (38·5% of 1503 cases) and Holm (1982) (50% of 142 cases). Volpe (1981) investigated 100 children with 'hypoxic ischemic encephalopathy' and found that 75% had a 'non-traumatic labor and delivery, and sustained the insult because of serious maternal disease and/or placental abnormalities'.

One of the commonest features of pregnancies which have resulted in cerebral palsy is the syndrome of relative infertility—fetal loss immediately before and following the pregnancy which led to cerebral palsy, or prolonged relative sterility before conception was achieved. Ingram & Russell (1961) found that a pregnancy contiguous to that resulting in the birth of a child with spastic diplegia was more often abnormal than a more remote pregnancy. Chefetz (1965) in his study of 275 children with cerebral palsy, found this 'reproductive inefficiency' in 78·4%.

Nelson (1968) reviewed the well-known work of Lilienfeld, Parkhurst and Pasamanick, which they described in 31 presentations in 20 journals over 11 years, concerning the prenatal history of cerebral palsy, convulsions, mental subnormality and other defects; they referred to the abnormal children, in controlled studies, as representing a 'continuum of reproductive wastage, with a lethal component consisting of abortions, stillbirths, neonatal deaths, and a sublethal component consisting of cerebral palsy and perhaps other related conditions'. The mothers of the children with cerebral palsy had approximately 35% more infant loss in pregnancies previous to the birth of a case of cerebral palsy than occurred in the general population.

It is probable that the age of the mother has little if any bearing on the incidence of 'brain damage', although Ingram & Russell (1961) and Durkin *et al.* (1976) thought that the older mother was slightly more at risk of having an affected child.

About a third of all children with cerebral palsy were of low birthweight. Hagberg *et al.* (1976) found that this was true of 30% of 200 children with hemiplegia and 41% of those with spastic diplegia. In many papers, including my own, the distinction was not drawn between preterm babies of weight appropriate to gestation and small-for-dates infants: the latter group is likely to contain infants who were growth retarded *in utero*, presumably due to impairment of nutrient supplies, a condition usually termed without evidence as 'placental insufficiency'. Preterm small-for-dates infants are at much greater risk than term small-for-dates infants. Atkinson & Stanley (1983) observed that the mean birthweight of children with spastic diplegia was less than that of unaffected children of the same gestational age, and the head circumference was smaller.

Intrauterine growth retardation is itself associated with a wide variety of circumstances. They include socioeconomic conditions, inadequate spacing of births, malnutrition, low maternal weight-gain, infections, diabetes, cardiovascular and renal disease, hypertension, pre-eclampsia, antepartum haemorrhage, placental infarction and separation, uterine anomalies, hydramnios, drug addiction (especially alcohol and smoking), irradiation, multiple pregnancy, twin transfusion syndrome, fetal chromosome and genetic abnormalities. Intrauterine growth retardation and fetal abnormalities have also been ascribed to toxic substances in pregnancy, e.g. mercury (Minamata disease) and anti-epileptic drugs.

Wagner & Arndt (1968) emphasized the important association of postmaturity and cerebral palsy. Twenty-eight per cent of 100 pregnancies leading to cerebral palsy had lasted 41 weeks or more, and 14% 42 weeks or longer.

Several papers from America, Australia, Sweden and Finland (Eastman & Deleon 1955; Hagberg *et al.* 1976; Dale & Stanley 1980) found a significantly higher incidence of antepartum haemorrhage and pre-eclampsia in mothers of children with cerebral palsy than in controls. Dale & Stanley (1980) found that 19·3% of 313 mothers of affected children had had a haemorrhage, but only 5 3% of controls. It is possible that some cases of antepartum haemorrhage followed by late handicaps are due to attempts to procure abortion.

Hyperthermia in pregnancy, known to be teratogenic in animals, has been blamed for human fetal neurological damage (Halperin & Wilroy 1978).

The genetic factor in cerebral palsy, other than that due to kernicterus in haemolytic disease, is often not recognized, but it is important (Ingram 1964). I reviewed many papers on this subject in 1958 (Illingworth 1958). In my own series of 760 children with cerebral palsy of prenatal or perinatal origin, excluding kernicterus, 4% had an affected sibling. This may be an underestimate because of the absence of autopsies on aborted fetuses and stillbirths in a family in which a case of cerebral palsy has occurred.

Pointers to other prenatal factors

The high incidence of congenital anomalies found in children with mental subnormality or cerebral palsy is a strong indication of a prenatal origin for many so called 'brain-damaged' children. In my own Sheffield study of 1068 mentally subnormal children excluding Down's syndrome, hypothyroidism, cerebral palsy or hydrocephalus, 30% had other congenital anomalies; the corresponding figure in 756 children with cerebral palsy was 7·7%. Eastman & Deleon (1955) found that 14% of 96 spastic children had congenital anomalies. The usual figure for congenital anomalies in babies is around 2%.

Another, often the only, indication of a prenatal origin for the handicap in these children is the frequent finding of a small head at birth in relation to the weight.

Another group of pointers to the prenatal origin of many cases of 'brain damage' has been provided by the examination of the teeth, rib ends and dermatoglyphics in affected children. Via & Churchill (1957) found that 68% of 100 children with cerebral palsy, but none of the controls, had enamel hypoplasia. All 12 children with spastic diplegia, all with athetosis and six of 14 children with spastic hemiplegia showed these changes. They found that knowing the chronological pattern of enamel growth, they could date the onset of the brain-damaging event. Cohen & Diner (1970) made similar observations, especially with regard to the timing of the cerebral insult.

Another method of dating prenatal insults was that of Emery & Kalpaktsoglou (1967). In their study of 5000 costochondral junctions, they found growth arrest or bizarre growth in the rib ends of children who had suffered intrauterine insults (e.g. antepartum haemorrhage or other maternal illness), and were able in many to date the insult.

A study of dermatoglyphics may point to the occurrence and timing of insults *in utero*. Martin *et al.* (1960) in a study of 175 cases of cerebral palsy, showed that the dermatoglyphics indicated a disturbance of fetal growth in the third or fourth month. Dar & Jaffé (1983) made similar observations in 300 moderately or severely retarded children. Preus & Fraser (1972) reviewed the literature, with 100 references.

Reviews of the pathology of cerebral palsy and 'brain damage' have almost without exception indicated the importance of prenatal maldevelopment or intrauterine hypoxia. Sigmund Freud in his book on cerebral palsy criticized Little's concept of birth injury, arguing that the preterm delivery, hypoxia or difficult labour were the result, not the causes, of the conditions which led to cerebral palsy. Emminger (1956), reviewing his

1084 autopsies on fetuses or infants, described 150 children who on account of fits and severe hypoxia had been diagnosed as having cerebral haemorrhage, but in which the diagnosis was not confirmed at autopsy. Even rupture of the tentorium was not related to the complications of birth. He wrote 'Birth *per se* is not the cause of these injuries (torn tentorium or falx or terminal vein), but merely discloses the presence of lesions produced during fetal development, rendering the fetus liable to suffer severe, generally fatal injury during the actual process of birth. The primary causative factors are lesions caused by anoxia during fetal development'.

Gross *et al.* (1968) in their histopathology studies of 891 cases of mental subnormality, wrote that if delivery is abnormal, it will inevitably be blamed for the cerebral defect. In 108 cases of cerebral palsy, the history suggested birth injury, but in at least a third no perinatal damage was found. In a third of all 'neuropathologically confirmed cerebral malformations, birth injury had been reported'. 'Organic cerebral damage is often only the sequel, but may have been the cause of a birth complication or apparent perinatal anoxia. In less than half the cases with reports of abnormal delivery was the morphological brain damage reasonably referrable to the birth injury'.

Prenatal hypoxia has been regarded by most of the reviewers as the predominant cause of 'brain damage' (Myers 1972, Pape & Wigglesworth 1979).

Many papers have shown that intracranial haemorrhage is a most unlikely cause of cerebral palsy. Pape & Wigglesworth (1979) wrote about the 'widespread agreement over the lack of association between abnormal delivery, other than preterm birth, and the development of intraventricular haemorrhages'. In the study of cerebral haemorrhage by Craig (1938) 30 of 126 children had had a normal delivery.

Unproved but possibly relevant prenatal factors

The possible role of the time of ovulation, and of a paternal contribution, has been largely ignored in studies of the aetiology of brain defects. Lanman (1968) in a series of three articles reviewed the experimental work on the effect of over-ripeness of the gamete in causing congenital abnormalities. Hecht (1975) and Guerrero & Rojas (1975) related the aging of human ova and spermatozoa to congenital malformations and mental subnormality. Furuhjelm *et al.* (1960) had previously related spermatozoal defects to perinatal mortality.

Advanced paternal age, after allowance for maternal age, has been linked to stillbirths (Woolf 1965), CNS defects other than spina bifida (Newcombe & Tavendale 1965), congenital malformations, Apert's syndrome, achondroplasia, a rare type of Down's syndrome and Del Castillo syndrome.

The effect of drugs and toxic substances on the spermatozoa or seminal fluid was reviewed by Joffe & Soyka (1982) and included amongst other substances, lead, methadone, agent orange, dioxin, alcohol, anticonvulsant and possibly anaesthetic agents. Evans *et al.* (1981) suggested that paternal smoking might cause chromosome damage, and Stenchever (1970) referred to chromosome damage by paternal antimetabolites and cannabis.

Labour and the process of birth

It would be absurd to suggest that brain damage cannot occur during labour or delivery; but there is much evidence to suggest that doctors and others are too ready to ascribe mental subnormality or cerebral palsy to such damage. Cardwell (1956) in her book on cerebral palsy concluded that 'faulty obstetric practice, formerly thought to be responsible for most of these cases, is now considered by some authorities to account for only 3 to 5% of the children'. Reger (1965) in his book *School Psychology*, noted that some 43 symptoms have been ascribed to birth injury. He concluded that 'there is no justification whatsoever to continue to call children brain-injured if there is no reason to assume that those children have injuries to the brain. Most of what is assumed to be known about the brain-injured child is folklore'. (In another paper at least 100 symptoms in children were ascribed to minimal brain damage.) It was pleasing to read in Britain's newest paediatric textbook that Kerr & Forfar (1984) wrote 'The idea that physical violence, possibly aggravated by the use of instruments, is a common cause of cerebral birth injury, has now been discounted. Indeed, the evidence is that the competent use of instruments, where necessary, in the delivery of the infant, prevents injury. Where injury occurs in association with a difficult and complicated delivery in which instruments have been used, such use is likely to have prevented even worse damage.'

In the Sheffield Jessop Hospital obstetric follow-up clinic, I was constantly impressed for a period of over 25 years by the fact that babies who had had an extremely difficult, complicated delivery were *not* the children who proved to have cerebral palsy or other detectable brain damage. This is the experience of others. Keith & Gage (1960) in a long-term follow-up of children born after prolonged labour or perinatal hypoxia, with a control group, found no increase of 'brain damage': none of the 321 children born after prolonged labour, and none of the 180 born after severe perinatal hypoxia, had neurological damage. Amiel-Tison (1969) in Paris followed 25 children who had severe neurological signs in the newborn period: none had cerebral palsy, but six were retarded. She wrote that 'the general impression that prenatal anomalies are responsible for the greater part of the severe definitive encephalopathies was confirmed'. Ounsted (1980) in Oxford discussed seven 'seriously brain damaged children'; only one had had significant perinatal problems.

There is much evidence, reviewed by Myers (1972), that prolonged moderate hypoxia *in utero* is of much greater significance to the fetus than an acute episode of severe hypoxia during delivery; and that the great majority of children who experienced severe perinatal hypoxia do not show evidence of brain damage, on long-term follow-up. In Denmark, Lenstrup (1964) followed 32 children who suffered severe hypoxia at birth: none had mental subnormality or cerebral palsy. Looking at it in another way, Berendes (1969) found that of 61 cases of cerebral palsy, 10 had passed meconium during labour, as compared with seven unaffected controls; five of the affected children and two of the controls had had a fetal heart rate of $\leqslant 100$ beats/min during labour. Steiner & Neligan (1975) followed, for a mean of 4½ years, 22 children who had sustained cardiac arrest at birth: none of those who had regular respirations by 20 to 30 min had cerebral palsy. Scott (1976) followed 48 severely hypoxic infants of whom 15 were stillborn and 33 had not established respiration by 20 min. Three to seven years later 17 of the 23 survivors were neurologically normal. Six had cerebral palsy, but two of them were small-for-dates and the other four had had prolonged moderate hypoxia.

Thomson *et al.* (1977) followed 39 children who had an Apgar score of 0 at 1 min or $\leqslant 4$ at 5 min; two of the 31 survivors were severely handicapped. De Souza & Richards (1978) followed 53 term infants who suffered fetal distress in labour and had severe neurological abnormalities in the newborn period. Two to five years later they were no different from matched controls. Nelson & Ellenberg (1981) in the American collaborative project, studied 120 children with cerebral palsy in which there was no known postnatal cause. Only 31 (26%) had an Apgar score of $\leqslant 3$ at 1 min, and 18 (15%) at 5 min. It follows that 89 of 120 children with cerebral palsy had an Apgar score of $\geqslant 4$ at 1 min, 66 (55%) had a score of $\geqslant 7$ at 1 min, and 85 (73%) at 5 min. Brann (1981) in a similar study found that an Apgar score of $\leqslant 3$ at 5 min was associated with cerebral palsy in only 1% of survivors.

It is evident that perinatal hypoxia was not the only cause of 'brain damage'—or that full recovery occurs in the majority. Relevant factors concerning the reversibility of possible damage must include the severity and duration of perinatal hypoxia, but also the presence of prenatal factors especially chronic intrauterine oxygen lack. Nevertheless, even though there has apparently been full recovery after severe hypoxia, minimal sequelae, such as defective spatial appreciation, may become manifest when the child is older.

Postnatal factors

It would be foolish to suggest that 'brain damage' or cerebral palsy is necessarily due to prenatal or perinatal factors, to which the main body of this paper is purposely devoted. The neonatal management, especially of the low-birthweight baby, may itself cause the damage or aggravate the effects of prenatal or perinatal factors. Relevant aspects of neonatal management include that of hypoxia, the respiratory distress syndrome, apnoeic and other respiratory problems, hypoglycaemia, acidosis, hypothermia, hyperbilirubinaemia, intraventricular haemorrhage and convulsions.

Postnatal management by the parents may also have a considerable bearing on the later progress of a handicapped child by alleviating or aggravating his problems.

Interaction of prenatal, perinatal and postnatal factors

In his book Ingram (1964) provided a detailed analysis of the many aetiological factors in cerebral palsy. Numerous papers confirmed or amplified Ingram's findings (e.g. Eastman &

Deleon 1955; Cardwell 1956; Durkin *et al.* 1976; Dale & Stanley 1980). Chefetz (1965) wrote that there is rarely just one cause in a case of cerebral palsy; there are nearly always multiple interacting factors. As Berendes (1969) put it, perinatal difficulties may be 'an insult on prepared soil'. Various workers (e.g. Emminger 1956; Drillien *et al.* 1964; Chefetz 1965; Gross *et al.* 1968; Michaelis *et al.* 1980) suggested that an underlying brain defect predisposed to perinatal problems, especially hypoxia. Drillien *et al.* (1964) found that a history suggestive of birth injury was obtained nearly three times as often when there had been relative infertility, as when fertility had been normal. In a previous paper concerning 279 children with spastic diplegia, Ingram & Russell (1961) wrote about 'the theory that underlying abnormalities of the reproductive process in mothers of diplegics may be responsible for both disorders of pregnancy, labour and delivery, and for the production of abnormal offspring'.

Pape & Wigglesworth (1979) suggested that intrauterine growth retardation may predispose to intraventricular haemorrhage at birth, and Scott (1976), Jurgens van der Zee *et al.* (1979) and Macdonald *et al.* (1980) suggested that it may predispose to perinatal hypoxia, as may maternal malnutrition. There is said to be an association between prematurity, pre-eclampsia and antepartum haemorrhage (Niswander *et al.* 1966). There are many causes of premature delivery, intrauterine growth retardation and 'placental insufficiency'.

Breech delivery is blamed for many cases of 'brain damage'. Dale & Stanley (1980) in Australia found that 11·5% of 313 children with cerebral palsy had been born by breech delivery, compared with 2·9% controls. But it is un-satisfactory to accept breech delivery as the cause of cerebral palsy without considering its causes or associated conditions—as reviewed by Braun *et al.* (1975); these include low birthweight, multiple pregnancy, hydramnios or oligohydramnios, placenta praevia, bicornuate uterus, the fetal alcohol syndrome, syndromes of Prader Willi, Smith Lemli Opitz, Potter, Zellweger, Werdnig-Hoffmann, Riley and de Lange, myotonic dystrophy, spina bifida, anencephaly, and trisomy 13, 18 and 21. Hytten (1982) suggested that a fetal neurological deficit which disrupts normal muscular control, may cause persistent leg extension and prevent the assumption of a normal fetal posture. Faber-Nijholt (1983) in his study of 281 children born by the breech, thought that the danger of breech presentation lay more in its causes than in the delivery.

I suggest that there is undue readiness to ascribe 'brain damage' to umbilical cord problems. I know that there is disagreement about this. Earn (1951) in Canada found a loop round the neck of the fetus in 23% of 5676 consecutive births; except in one case in which there were eight loops, the children were unaffected. Shui (1957) in Hongkong found a nuchal loop in 20% of 1000 deliveries—with no damage to the fetus. Crawford (1962) and Horwitz *et al.* (1964) found that there was no increased death rate unless the cord was ligated before birth; Horwitz *et al.* (1964) found that all 10 cases in which there was a true knot were unharmed.

Cushner (1961) reviewed cases of cord prolapse: 60 of 63 infants were unharmed. There is a danger of compression of the cord, and the prolapse may be unrecognized (Niswander *et al.* 1966). Cushner (1961) noted the conditions associated with prolapse of the cord—abnormal presentation, low birthweight, multiple pregnancy, placenta praevia, obstetric manipulations and pelvic disproportion.

Chefetz (1965) found no association between the 275 cases of cerebral palsy and umbilical cord problems; Steer & Bonney (1962) found the same in their 276 cases of cerebral palsy.

Multiple pregnancy increases the risk of brain damage. In my series of 651 cases of cerebral palsy, 8·4% arose from multiple pregnancy. Related factors include preterm delivery, abnormal presentation, prolapse of the cord and the twin transfusion syndrome—which carries a high risk of fetal and neonatal death with anoxic damage to one twin (Raussen *et al.* 1965).

Discussion

The causes of cerebral palsy, mental subnormality and so-called 'brain damage' are numerous and complex, and interact with each other. As with so many medical problems, features of 'brain damage' are the end result of a wide variety of pathological processes. When the causes are so complex, it is not only unscientific (in most cases) to ascribe a child's neurological handicap to a single event at birth, calling it 'birth injury' or 'brain damage', but it is undesirable for the parents, who are then bound to blame the obstetrician or midwife. If a tragedy befalls any of us, it is better that we should feel that it was unavoidable, rather than to feel that it was due to someone's carelessness or negligence.

For many reasons it is difficult to interpret scores of papers on the subject: they include inaccurate or imprecise definition of such terms as 'fetal distress', 'cerebral palsy', 'brain damage', 'antepartum haemorrhage', 'toxaemia'; inadequacy or inaccuracy of special investigation such as failure to exclude infections, or a possible paternal component. Most, but not all, of the studies were retrospective, and frequently the duration or quality of follow-up was inadequate. Often there was a failure to look behind the obvious factor, such as hypoxia at birth, neonatal convulsions or breech delivery, to the causes of those conditions. There was a marked tendency to accept that there was no birth injury, because delivery was normal, or to accept that there were no neonatal factors, because none was obvious. The absence of controls and of prospective studies present great difficulty; one would like to know how many women have, or do not have, the many prenatal, perinatal or neonatal risk factors, and have normal or handicapped children. For instance, there is much evidence that antepartum haemorrhage is a 'risk factor', but one needs to know how many have antepartum haemorrhage and then have a normal child.

Some of the needs for future research can be divided into the prenatal, perinatal and postnatal services. One needs to identify by the newer sophisticated techniques the children at risk. Rayburn *et al.* (1981) found that of 168 children who had been admitted to the intensive care unit, the need had been anticipated in only 59 (35%). They concluded that the need for intensive care frequently cannot be predicted till labour or delivery.

If there are risk factors, we need to know what can be done, if anything, to make delivery safer—to avoid adding the last straw for a high-risk baby. We need to know more about the value of investigation and treatment in the prenatal period; we have to ask the questions 'What good will the investigation do? What harm may it do? What harm may be done by not doing it?'

In the perinatal period we need to know more about the different methods of management, e.g. caesarean section for breech deliveries—again asking the questions 'What good may it do (as compared with vaginal delivery)? What harm may it do? What harm may result from not doing it?'

The many newer methods of management of the newborn infant, especially the extreme preterm, need urgent study, with special regard to the undesirable side-effects of treatment such as umbilical vessel cannulation, the risks of a radial line, positive pressure ventilation, or oxygen concentration in relation to cerebral palsy, retrolental fibroplasia: and above all, we need adequate follow-up so that one can determine the risks of all methods of management in relation to subsequent handicap.

One feels that the risk factors, prenatal, perinatal and postnatal, are so numerous, complex, and interwoven that computer studies are essential. That presents financial problems, but a teaching hospital should be able to face them.

It is simplistic, irrational and naïve to ascribe cases of mental subnormality, cerebral palsy, or other features of 'brain damage' to birth, just because birth, always dangerous, is one possible factor, or just because some aspect of management can be criticized, though many would regard it as acceptable. It is not sensible to blame the obstetrician or midwife, without considering all the other possible factors which might have caused or greatly aggravated the difficulties of delivery.

The motto of the University of Sheffield is '*Rerum cognoscere causas*'; but I prefer the entire line from Virgil, which reads '*Felix qui potuit rerum cognoscere causas*'—'happy is the man who is able to discover and understand the causes of things'.

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Pre-eclampsia in second pregnancy

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Summary. A total population of pregnant women from Aberdeen City District 1967–1978 has been studied. There were 29 851 pregnancies and 6637 women had a first recorded pregnancy between 1967 and 1978 and had two or more pregnancy events. As expected the incidence of pre-eclampsia in a second pregnancy was less than that in a first pregnancy, but it was dependent on the outcome of the first pregnancy. If the first pregnancy was complicated by proteinuric pre-eclampsia than the incidence of the condition in the second pregnancy was similar to that in a first pregnancy, but women who were normotensive in the first pregnancy had a reduced incidence of the condition in the second pregnancy. The incidence of proteinuric pre-eclampsia after early abortion (<13 weeks), either spontaneous or induced was similar to the population incidence in a first pregnancy, but after a late spontaneous abortion the risk of proteinuric pre-eclampsia was significantly reduced. Change of civil status of the offspring from first to second pregnancy did not affect the incidence of pre-eclampsia in a second pregnancy. There was an effect of birthweight in that women who had proteinuric pre-eclampsia in conjunction with a low-birthweight baby (<2500 g) in their first pregnancy had double the incidence of proteinuric pre-eclampsia in their second pregnancy. Only a pregnancy of 37 weeks or more is likely to offer protection or 'immunity' to pre-eclampsia in a second pregnancy and even then the effect is moderated by the development of pre-eclampsia in the first pregnancy.

It has generally been accepted that pre-eclampsia is a disease of first pregnancy. MacGillivray (1958) showed that the risk of severe pre-eclampsia was 15 times greater in a first than in a second pregnancy. In addition, he showed that the risk was dependent on the outcome of the first pregnancy. Thus, proteinuric pre-eclampsia in a second pregnancy was commoner when proteinuric pre-eclampsia was present in a first pregnancy, and a spontaneous abortion in the first pregnancy reduced the incidence in a subsequent pregnancy, but not so dramatically as a full length pregnancy.

A multicentre World Health Organization-sponsored study (J. Belsey 1983, personal communication) to follow-up pregnancies subsequent to a previous termination of pregnancy suggested that, overall, pre-eclampsia was less prevalent in the following pregnancy. But the incidence in previous and subsequent pregnancies varied substantially from centre to centre and the centres did not use the same or even a similar definition of pre-eclampsia.

Moreover, it is a clinical impression that, when pre-eclampsia occurs in a second pregnancy, the obstetric outcome is not so severe in

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terms of preterm delivery, low birthweight, or perinatal death but, as far as the authors are aware, there has been no systematic investigation of this This paper sets out to examine further the occurrence of pre-eclampsia in a second pregnancy, both in terms of its severity and its antecedent factors.

Subjects and methods

The data used were obtained from the Aberdeen Maternity and Neonatal Data Bank (Samphier & Thompson 1982). The population under review was the total population of women from Aberdeen City District delivered between 1967 and 1978.

During this period there were 29 851 pregnancies recorded and, of those, 6637 women had a first recorded pregnancy between 1967 and 1978 *and* had two or more completed pregnancies. It is on this latter group that the majority of the analysis has been performed. The results are presented for a variety of subgroups of these women (e.g. those with pregnancies terminating on or before the 27th week, or those with pregnancies going to the 28th week or beyond, in either the first or second pregnancy) so that the total numbers vary from table to table. This will be indicated where appropriate.

It is important to emphasize that, with the exception of Table 1, this study was restricted to the *first two pregnancies only* whatever their outcome, and, in particular, whether they terminated before or after the 28th week of gestation. To distinguish pregnancies terminating on or before the 27th week from those continuing to the 28th week or beyond, we have called the latter viable-first, or viable-second pregnancies Note that, with this nomenclature, a second pregnancy of ≥28 weeks following an aborted first pregnancy will be called a viable-second pregnancy, even though it is the first pregnancy event with a viable outcome.

Pre-eclampsia has been defined according to Nelson (1955): hypertension was defined as a diastolic blood pressure of ≥90 mmHg occurring after 26 weeks gestation on two consecutive occasions at least 24 h apart, or a progressive rise to ≥90 mmHg or more in labour, severe or proteinuric pre-eclampsia was defined as hypertension plus proteinuria of >0·25 g/l. Trace amounts of protein in the urine were considered insignificant and such cases have been included as mild pre-eclampsia All women were coded for pre-eclampsia at the time of their pregnancies and recorded as such in the data bank. Eclampsia was defined as convulsions, antepartum, intrapartum or postpartum, not due to other causes such as epilepsy.

The first part of the paper describes the incidence of pre-eclampsia and the outcome of pregnancy in the first and second pregnancies (Tables 2–5). The focus here is on the relative severity of pre-eclampsia in first and second pregnancies so that the comparison of interest is between the pregnancy outcomes for the same category of pre-eclampsia in first and in second pregnancy.

In the second part of the paper we turn to the investigation of whether the likelihood of pre-eclampsia in a second pregnancy is conditional on *either* the occurrence of pre-eclampsia in a viable first pregnancy (analysed by gestation, birthweight and civil status), or, when the first pregnancy terminated before 28 weeks, the kind of abortion and the stage at which the pregnancy was terminated. The problem here is whether or not a particular feature of a first pregnancy influences the occurrence of pre-eclampsia in women who are having a second pregnancy. The comparisons of interest are, therefore, between sub-

Table 1. Percentage incidence of pre-eclampsia by pregnancy number

Pregnancy no	Total no	Eclampsia %(*n*)	Proteinuric pre-eclampsia %(*n*)	Mild pre-eclampsia %(*n*)	Normotensive %(*n*)
1	11534	0·1 (14)	6·1 (706)	27·5 (3177)	66·2 (7637)
2	9730	0·0 (3)	1·9 (184)	17·7 (1719)	80·4 (7824)
3	5002	0·1 (3)	1·2 (62)	15·7 (785)	83·0 (4152)
4	2155	0·0 (1)	0·6 (13)	15·9 (343)	83·4 (1798)
5–15	1430	0·0 (0)	1·1 (16)	18·0 (257)	80·9 (1157)
All pregnancies	29851	0·1 (21)	3·3 (981)	21·0 (6281)	76·6 (22568)

Based on all pregnancies in Aberdeen City District between 1967 and 1978.

groups of women defined in terms of specific features of their first pregnancy and *not* between women having their first as against their second pregnancy.

This is an important distinction as it raises the question of what is meant in this paper by the degree of protection afforded to a woman having her second pregnancy. In one view, which is close to the classical idea of immunization, the condition of proteinuric pre-eclampsia is like a deficiency condition, so that those who contract it once (on, for example, a first pregnancy) are almost certain to contract it again (for example, on the second pregnancy). According to this interpretation, 'protection' in the second pregnancy would refer to *any* reduction of the incidence *for that group who contracted it on the first pregnancy* below 100%. If this is taken seriously, then *any* kind of first pregnancy provides substantial protection to women in the second pregnancy; as our study shows, there is no subgroup (defined in terms of the characteristics of the first pregnancy) for whom the incidence on the second pregnancy is higher than 13·0% (see below) so that even this particular subgroup have been 'immunized' to a level of 87%. We have taken the view that variations in the level of protection above 87%, whilst of importance, are not the most interesting statistics. Instead, the alternative view is adopted in this paper whereby proteinuric pre-eclampsia is thought of as similar to an infectious disease occurring 'at random' in a population of pregnant women. Hence, on this interpretation the statistic of interest is the *degree of 'protection'* when assessed *relative to the first pregnancy*.

In other words, whilst we are indeed interested in which characteristics of the first pregnancy differentiate groups of women with different risks of pre-eclampsia in the second pregnancy, the crucial test is whether the incidence in the *second* pregnancy, for any particular group of women (however defined) approaches the population incidence on the first pregnancy (as given in Tables 1 or 3). Hence, because the population incidence in the second pregnancy is, overall, low compared to that in the first pregnancy (see Tables 1 or 3) a particular group of women may have a high risk in the second pregnancy *relative to other women having their second pregnancy*, but still have gained a *measure of protection* (from their reproductive history or whatever) relative to the population incidence in the first pregnancy.

Results

The presentation of results concentrates on the incidence of and the recurrence of pre-eclampsia. The numbers with eclampsia are so small that (apart from Tables 1–3) they have been considered separately at the end of this section.

The first set of tables (Tables 1–5) record the incidence of pre-eclampsia in the first and second pregnancies separately, analysed by various characteristics. Table 1 shows the incidence of mild and proteinuric pre-eclampsia and of eclampsia according to pregnancy number for all 29 851 pregnancies delivered in Aberdeen City District between 1967 and 1978. It can be seen that the incidences of both mild and proteinuric pre-eclampsia decreased from first pregnancy to second pregnancy and again from second pregnancy to third pregnancy whilst the incidence of eclampsia decreased from the first to second pregnancy. After the third pregnancy, although the difference in the incidences of proteinuric pre-eclampsia between third and fourth pregnancies and between fourth and fifth pregnancy were both statistically significant ($P<0·05$) they were in opposite directions so there is no obvious trend. Finally, we note that the biggest decreases, both absolutely and relatively, occurred between the first and second pregnancy which was consistent with other studies.

Table 2 compares the pregnancy outcomes in first and second pregnancies for the 6637 women who are the focus of this paper. It can be seen that they are quite similar except that the proportion of abortions (taking spontaneous and

Table 2. Outcome of first and second pregnancies in the basic study population

Obstetric outcome	First pregnancy %	(*n*)	Second pregnancy %	(*n*)
Live singleton	87·2	(5784)	85 0	(5643)
Stillbirth	1·0	(69)	0·7	(46)
Multiple pregnancy	0·4	(25)	0·9	(60)
Spontaneous abortion	5·1	(335)	7·8	(517)
Induced abortion	6·3	(419)	5·4	(358)
Other	0 1	(5)	0·2	(13)
Total		(6637)		(6637)

All women in Aberdeen City District whose first recorded pregnancy took place between 1967 and 1978 and had two or more completed pregnancies in that period.

induced together) has increased from 11·4% to 13·2%—a statistically significant increase ($P<0·05$).

Pre-eclampsia is itself a disease occurring in the last trimester of pregnancy so its incidence is only properly compared as between those women whose pregnancies continue to 28 weeks or beyond. Excluding spontaneous and induced abortions, ectopics and moles from the first and second pregnancies *separately*, reduces the 6637 women to 5878 in the first pregnancy and 5749 in the second pregnancy. Table 3 shows the relative incidence of pre-eclampsia in first and second pregnancies in these women. It can be seen that the incidences of both mild and proteinuric pre-eclampsia and their decrease from first to second pregnancies are very similar to the population values given in Table 1.

Table 3. Incidence of pre-eclampsia during 5878 viable first and 5749 viable second pregnancies in the basic study population

Degree of pre-eclampsia	First pregnancy %	(*n*)	Second pregnancy %	(*n*)
Normotensive	68·0	(3998)	81·3	(4673)
Mild pre-eclampsia	26·3	(1541)	17·0	(965)
Proteinuric pre-eclampsia	5·6	(329)	1·9	(110)
Eclampsia	0·2	(10)	0·0	(1)
Total		(5878)		(5749)

Basic population as in note to Table 2 excluding, *separately for each pregnancy*, pregnancies which did not reach 28 weeks.

It is, however, important to compare the relative severity of the different degrees of pre-eclampsia in the first and second pregnancies in terms of outcome and this is shown in Tables 4 and 5. Note that both tables exclude the women who contracted eclampsia (10 in the first pregnancy and one in the second) reducing the totals to 5868 and 5748 respectively and that Table 5 further excludes multiple pregnancies, stillbirths and those for whom the gestation was not known, reducing the totals still further to 5695 and 5465 respectively.

Table 4 shows the number of perinatal deaths according to the degree of pre-eclampsia. The overall perinatal death rate was 11·8/1000 in the first pregnancy and 8·0/1000 in the second pregnancy, the kind of decrease that would be expected between first and second pregnancy. The rates are, however, at least three times higher in those women with proteinuric pre-eclampsia when compared with the other women in both first and second pregnancies (33·4/1000 compared with 10·4/1000, and 27·3/1000 compared with 7·6/1000 respectively.

Table 5 shows the association between preterm delivery and the degree of pre-eclampsia in first and in second pregnancies separated according to whether or not the labour started spontaneously. The overall rates of preterm delivery were 4·3% in the first pregnancy and 3·2% in the second pregnancy; considering spontaneous labours only, the rates were 6·5% and 4·1% respectively. It can be seen, however, that the likelihood of a preterm delivery was much higher in those with proteinuric pre-eclampsia and consistently lower in those with mild pre-eclampsia. For example, in the group of 3285 women who entered labour spontaneously in the first pregnancy, preterm delivery occurred in 13 of the 99 with proteinuric pre-eclampsia (13·1%), in 30 of the 655 with mild pre-eclampsia (4·6%) and in 171 of the 2531 normotensive women (6·8%). As expected, mild pre-eclampsia was mainly a condition of late pregnancy whilst proteinuric pre-eclampsia was associated with early delivery—and similar patterns were observed in the other groups in Table 5.

It might be thought that there is a stronger association between pre-eclampsia and preterm

Table 4. Perinatal deaths by pre-eclampsia status in 5868 first and 5748 second pregnancies

Degree of pre-eclampsia	First pregnancy Total births	First pregnancy Perinatal deaths *n*	First pregnancy Perinatal deaths Rate/1000	Second pregnancy Total births	Second pregnancy Perinatal deaths *n*	Second pregnancy Perinatal deaths Rate/1000
Proteinuric pre-eclampsia	329	11	33·4	110	3	27·3
Mild pre-eclampsia	1541	16	10.4	965	7	7·3
Normotensive	3998	42	10·5	4673	36	7·3
Total	5868	69	11·8	5748	46	8·0

Population as in Table 3, but excludes eclampsia—10 in first pregnancy and one in second.

Table 5. Length of gestation and pre-eclampsia in first and second pregnancy for singleton livebirths only

Pregnancy outcome	Gestation (weeks) 1–27 %(*n*)	 28–36 %(*n*)	 37-45 %(*n*)	 Total %(*n*)
First pregnancy				
All patients	(40)	(246)	(5409)	(5695)
Proteinuric pre-eclampsia	0	12·2 (30)	5 2 (279)	5·4 (309)
Mild pre-eclampsia	0	14.6 (36)	27·0 (1458)	26·2 (1494)
Normotensive	100 (40)	73·2 (180)	67·9 (3672)	68·2 (3892)
Spontaneous labours only	(7)	(214)	(3064)	(3285)
Proteinuric pre-eclampsia	0	6·1 (13)	2·8 (86)	3·0 (99)
Mild pre-eclampsia	0	14·0 (30)	20·4 (625)	19·9 (655)
Normotensive	100 (7)	79·9 (171)	76·8 (2353)	77·0 (2531)
Second pregnancy				
All patients	(18)	(174)	(5273)	(5465)
Proteinuric pre-eclampsia	0	6·3 (11)	1 6 (86)	1·8 (97)
Mild pre-eclampsia	0	10.3 (18)	17·1 (901)	16·8 (919)
Normotensive	100 (18)	83·3 (145)	81·3 (4286)	81·4 (4449)
Spontaneous labours only	(4)	(160)	(3776)	(3940)
Proteinuric pre-eclampsia	0	5·0 (8)	1·0 (37)	1·1 (45)
Mild pre-eclampsia	0	10·0 (16)	14·3 (541)	14 1 (557)
Normotensive	100 (4)	85·0 (136)	84·7 (3198)	84 7 (3338)

Population as in Table 4, but excludes separately for each pregnancy number, multiple pregnancies, still births and cases where gestation was not known.

delivery in the second pregnancy than in the first pregnancy. Thus, of the 246 preterm deliveries in the first pregnancy, 12·2% had proteinuric pre-eclampsia whereas of the 174 preterm deliveries in the second pregnancy, 6·3% had proteinuric pre-eclampsia. It is known, however, that women with proteinuric pre-eclampsia are more likely to be induced (and, therefore, delivered preterm) for either maternal or fetal reasons. Indeed, in the present data, of the 309 women with proteinuric pre-eclampsia in the first pregnancy, 210 (68·0%) were induced and of the 97 women with proteinuric pre-eclampsia in the second pregnancy, 48 (49·5%) were induced. Comparing the preterm deliveries after spontaneous labours in the first pregnancy with those in the second pregnancy (Table 5) shows that the incidences of proteinuric pre-eclampsia were essentially the same in the two groups [6·1% (13 of 214) and 5·0% (8 of 160) respectively].

The second set of tables (Tables 6–10) show the relation between the occurrence of pre-eclampsia in the second pregnancy analysed according to various characteristics of the first pregnancy. It should be noted that, in every case, the tables are restricted to those 5738 women with a viable-second pregnancy (as in Table 3, but excluding the 11 women who had eclampsia in either the first or second pregnancy). There are further distinct restrictions in each of the tables: so that Tables 6, 7 and 9 include data only on the 5125 women whose first and second pregnancy continued to the 28th week and Tables 8 and 9 exclude missing values; Table 7 is restricted to those who had an abortion in their first pregnancy, and Table 10 to those women whose civil status has changed between the two pregnancies.

Table 6 gives the incidence of pre-eclampsia in the second pregnancy according to the development of the condition in the first pregnancy. We recall that in second pregnancies among this population there were 1·9% with proteinuric pre-eclampsia and 17·0% with mild pre-eclampsia. It can be seen that those who had proteinuric pre-eclampsia in the first pregnancy had a greatly increased risk of both categories of pre-eclampsia in the second pregnancy (7·5% proteinuric and 30·1% mild); those who had mild pre-eclampsia in the first pregnancy had roughly the same risk of proteinuric pre-eclampsia and an increased risk of mild pre-eclampsia in the second pregnancy (2·0% and 29·0% respectively); and those whose first pregnancy was normotensive had a greatly reduced

Table 6. Pre-eclampsia in a viable second pregnancy by the occurrence of pre-eclampsia in the 5125 singleton viable first pregnancies

		Second pregnancy		
First pregnancy	*n*	Proteinuric pre-eclampsia % (*n*)	Mild pre-eclampsia % (*n*)	Normotensive % (*n*)
Proteinuric pre-eclampsia	279	7·5 (21)	30·1 (84)	62·4 (174)
Mild pre-eclampsia	1339	2·0 (27)	29·0 (388)	69·0 (924)
Normotensive	3507	0·7 (24)	9·3 (325)	90·1 (3158)
Total	5125	1·4 (72)	15·6 (797)	83·0 (4256)

Population is the subset formed by the intersection of the viable first and viable second pregnancy population defined in the note to Table 4, that is, the population where *both* pregnancies were viable.

Table 7. Pre-eclampsia in viable second pregnancy when the outcome of the first pregnancy was an abortion (*n*=589)

		Second pregnancy		
First pregnancy	*n*	Proteinuric pre-eclampsia % (*n*)	Mild pre-eclampsia % (*n*)	Normotensive % (*n*)
Spontaneous abortion				
≤12 weeks	170	7·6 (13)	28·2 (48)	64·1 (109)
13–27 weeks	120	1·7 (2)	31·7 (38)	66·7 (80)
Unknown	22	0	22·7 (5)	77·3 (17)
Total	312	4·8 (15)	29·2 (91)	66·0 (206)
Induced abortion				
≤12 weeks	153	7·8 (12)	26·1 (40)	66·0 (101)
13–27 weeks	103	7·8 (8)	27·2 (28)	65·0 (67)
Unknown	21	4·8 (1)	28·6 (6)	66·7 (14)
Total	277	7·6 (21)	26·7 (74)	65·7 (182)

Population is that subset formed by the intersection of the 754 women whose first pregnancy ended in an abortion (see Table 2) and the viable second pregnancy population defined in the note to Table 4.

risk of pre-eclampsia (compare 0·7% with 1·9% and 9·3% with 17·0%). Two points should be noted: it is true that those who had proteinuric pre-eclampsia in their first pregnancy were much more likely than any other group of women to contract proteinuric pre-eclampsia in the second pregnancy—indeed, their pattern of incidence of pre-eclampsia in the second pregnancy was 'worse' than that of the population first pregnancy incidence (compare percentages 7·5, 30·1, 62·4 with 5·6, 26·3, 68·0 in Table 3) and that whilst the degree of proteinuric pre-eclampsia in the second pregnancy was considerably less than the population first pregnancy incidence (compare 2·0% with 6·1%), the substantial 'protective' effect against pre-eclampsia in the second pregnancy occurred in those women whose first pregnancy was normotensive.

Table 7 examines the incidence of the different forms of pre-eclampsia in the second pregnancy when the first pregnancy terminated in either a spontaneous or an induced abortion. The incidence of proteinuric pre-eclampsia in the second pregnancy after either a spontaneous abortion (4·8%) or an induced abortion (7·6%) in the first pregnancy was much greater than the population incidence of 1·9% in the second pregnancy, and was very similar to the overall incidence of 6·1% in all first pregnancies (Table 1) and also to the incidence of 5·6% in a viable first pregnancy in this population (Table 3). It has, however, been suggested that the longer the duration of the first pregnancy, the greater might be the degree of protection (MacGillivray 1958). Table 7 also shows the incidence of pre-eclampsia in the second pregnancy after a spon-

Table 8. Pre-eclampsia in viable pregnancy by gestation of 4834 first pregnancies ending in a singleton livebirth

			Second pregnancy		
First pregnancy	Gestational age (weeks)	*n*	Proteinuric pre-eclampsia % (*n*)	Mild pre-eclampsia % (*n*)	Normotensive % (*n*)
Normotensive	1–27	16	0	43 8 (7)	56·2 (9)
	28–36	147	1·4 (2)	6·1 (9)	92·5 (136)
	37–45	3144	0·7 (21)	9·3 (293)	90·0 (2830)
Mild pre-eclampsia	1–27	0	0	0	0
	28–36	28	0	21·4 (6)	78·6 (22)
	37–45	1242	2 1 (26)	29·1 (361)	68·9 (855)
Proteinuric pre-eclampsia	1–27	0	0	0	0
	28–36	23	13·0 (3)	39·1 (9)	47·8 (11)
	37–45	234	6 8 (16)	29·5 (69)	63·7 (149)
Total	1–27	16	0	(7)	(9)
	28–36	198	(5)	(24)	(169)
	37–45	4620	(63)	(723)	(3834)

Population as in Table 6, but excludes women whose viable first pregnancy ended in multiple pregnancy or a stillbirth, or when the gestation was not known

Table 9. Pre-eclampsia in a viable second pregnancy by birthweight of 5059 first pregnancies ending in a singleton livebirth

			Second pregnancy		
First pregnancy	Birthweight (g)	*n*	Proteinuric pre-eclampsia % (*n*)	Mild pre-eclampsia % (*n*)	Normotensive % (*n*)
Normotensive	<2500	235	1 7 (4)	8·5 (20)	89·5 (211)
	≥2500	3227	0·6 (20)	9 0 (290)	90·4 (2917)
Mild pre-eclampsia	<2500	72	2·8 (2)	27·8 (20)	69·4 (50)
	≥2500	1257	2·0 (25)	29·0 (364)	69 1 (868)
Proteinuric pre-eclampsia	<2500	42	11 9 (5)	28·6 (12)	59·5 (25)
	≥2500	226	6 6 (15)	30·1 (68)	63·3 (143)
Total	<2500	349	(11)	(52)	(286)
	≥2500	4710	(60)	(722)	(3928)

Population as in Table 6, but excludes women whose viable first pregnancy ended in a multiple pregnancy, a stillbirth of where the birthweight was not known

Table 10. Pre-eclampsia in viable second pregnancy by pre-eclampsia in viable first pregnancy for 394 women who changed civil status

		Second pregnancy		
First pregnancy	*n*	Proteinuric pre-eclampsia % (*n*)	Mild pre-eclampsia % (*n*)	Normotensive % (*n*)
Proteinuric pre-eclampsia	26	3·9 (1)	26·9 (7)	69·2 (18)
Mild pre-eclampsia	92	3·3 (3)	17·4 (16)	79·3 (73)
Normotensive	276	0·4 (1)	10·5 (29)	89·1 (246)
Total	394	1·3 (5)	13·2 (52)	85·5 (337)

Population as in Table 6 for the subset where the recorded civil status of the baby changed from illegitimate to legitimate or vice versa between first and second pregnancy taneous or induced abortion analysed according to whether the abortion was early (<13 weeks) or late (13–27 weeks). The incidences of proteinuric and mild pre-eclampsia in a viable-second pregnancy after an early spontaneous abortion (7·6 and 28·2%) or after an induced abortion (7·6 and 26·7%) are similar to the incidences in viable first pregnancies reported in Table 3 (5·6 and 26·3%). The only apparent 'protection' occurs after a late spontaneous abortion against proteinuric pre-eclampsia where the difference between 1·7% and the population incidence in a viable first pregnancy of 5·6% is just significant (*P*=0·047).

Table 8 shows the effect of length of gestation in a viable first pregnancy on the incidence of pre-eclampsia in a viable second pregnancy. The incidence of preterm delivery in the first pregnancy among this population was 4·9% in normotensive women, 2·2% in those with mild pre-eclampsia and 8·9% in those with proteinuric pre-eclampsia (see also Table 5). Whilst the risk of proteinuric pre-eclampsia in the second pregnancy was increased from 1·3% to 2·5% if the first pregnancy did not go to term, the risk of mild pre-eclampsia was reduced from 15·5% to 12·0%.

When the first pregnancy had proteinuric pre-eclampsia, the already high incidence of proteinuric pre-eclampsia in the second pregnancy was nearly doubled (from 6·8% to 13·0%) if the first pregnancy ended before 37 weeks rather than if it went to term, *and* there was also a greater risk of mild pre-eclampsia. However, there was no consistent effect of gestation apparent when the first pregnancy was either normotensive or had mild pre-eclampsia. Thus, the effects of the length of gestation and of the degree of pre-eclampsia in the first pregnancy on the risk of pre-eclampsia in a second pregnancy were not cumulative but were concentrated among those women whose first pregnancy was proteinuric *and* preterm.

Table 9 shows the effect of birthweight in the first pregnancy on the incidence of pre-eclampsia in the second pregnancy. (The incidence of low birthweight among these viable first pregnancies was 6·8% if the pregnancy was normotensive, 5·4% if the woman had mild pre-eclampsia, and 15·7% if the woman contracted proteinuric pre-eclampsia.) The risk of proteinuric pre-eclampsia in the second pregnancy was much higher if the first pregnancy was associated with low birthweight (3·2% compared with 1·2%) whilst the risk of mild pre-eclampsia was unchanged (14·9% and 14·3%).

When the first pregnancy had proteinuric pre-eclampsia, the incidence of proteinuric pre-eclampsia in the second pregnancy was doubled if the first pregnancy ended with a birthweight <2500 g, but the risk of mild pre-eclampsia was slightly reduced. But, in contrast to length of gestation in the first pregnancy, low birthweight (<2500 g) in a first pregnancy which was either normotensive of mild pre-eclampsia did slightly increase the likelihood of proteinuric pre-eclampsia, although the likelihood of mild pre-eclampsia was unchanged. Note that none of these differences were statistically significant.

Finally, of the 10 women who had eclampsia in their first pregnancy, one had a termination, seven had singleton livebirths and two had twin pregnancies. The woman who had a termination in her first pregnancy, had a normotensive second pregnancy with a singleton livebirth. Of the seven eclamptics with singleton livebirths in their first pregnancy, five were normotensive and two developed mild pre-eclampsia in their second pregnancies and all had singleton livebirths again. The two women who had twin pregnancies with eclampsia in their first pregnancy both had singleton livebirths in their second pregnancy, one was normotensive and one developed mild pre-eclampsia. The only woman who had eclampsia in her second pregnancy with a singleton livebirth had previously had a normotensive first pregnancy with a singleton livebirth.

Discussion

A significant number of women who have proteinuric pre-eclampsia in their first pregnancy have proteinuric pre-eclampsia in their second pregnancy (Tables 1 and 2), and the rates of perinatal mortality and preterm delivery for them are about the same as if they had it in their first pregnancy (Tables 4 and 5). However, the incidence of pre-eclampsia in a second pregnancy is dependent on the pre-eclampsia status of the first pregnancy (Table 6). There is a greatly reduced risk in a second pregnancy when the first pregnancy was normotensive.

The early findings of a much higher incidence in first pregnancy relative to the second (MacGillivray 1958), a first pregnancy of short duration offering protection in a subsequent pregnancy (MacGillivray 1958) and the suggestion that a change of partner may alter the recurrence risk (Need 1975; Feeney 1980; Ikedife 1980) has prompted the search for an immunological aetiology in pre-eclampsia.

The findings of the present study only partially confirm these earlier results. First, the overall incidence of proteinuric pre-eclampsia in a second pregnancy in Aberdeen is higher now than it was before 1958. One possibility is that some patients might have been missed, accounting for the very low rate of pre-eclampsia if frequent urine tests and blood pressure measurements had not been routine for all multiparae at that time. Another possibility is that there may have been more blood transfusions in the 1950s and it had been suggested that this offers protection against pre-eclampsia in primigravidae (Feeney *et al.* 1977).

Second, in contrast to the earlier findings that a pregnancy of any duration confers some immunity in a subsequent pregnancy, this study shows that neither a spontaneous abortion nor an induced termination offers any substantial protection relative to the rates for a first pregnancy (compare Tables 7 and 3), the only possible exception being a late spontaneous abortion. Indeed, our findings suggest that whilst the risk of proteinuric pre-eclampsia in the second pregnancy is reduced relative to the first for women who had a viable first pregnancy ending in a singleton livebirth, the only substantial protection is conferred by a pregnancy continuing to 37 weeks or more—and even then the risk of pre-eclampsia in the second pregnancy is dependent on the pre-eclampsia status in the first (Table 8).

There was interestingly, however, a consistent, although small, effect of birthweight within categories of pre-eclampsia; in particular, those women who had low-birthweight babies and had proteinuric pre-eclampsia in a first pregnancy had double the incidence in their second pregnancy (Table 9). This might suggest that the women with the most severe pre-eclampsia at the same time as a significant retardation of fetal growth are the ones who are likely to have a recurrence in second pregnancy. Note that low birthweight in the first pregnancy had no influence on the risk of mild pre-eclampsia in the second, which is consistent with other findings that birthweight is not affected by hypertension alone (MacGillivray & Campbell 1980).

The third suggestion in the literature is that possible changes of partner between pregnancies increases the risk of pre-eclampsia in a second pregnancy. Whilst it was not possible for us to examine this directly, the civil status of the women is recorded in the data bank. We have, therefore, investigated 394 women for whom the civil status of their offspring was changed from the first to the second pregnancy (either from legitimate to illegitimate or *vice versa*) on the assumption that there would be many more women with a change of partner from first to second pregnancy in this group than there would be in the total population. Table 10 gives the incidence of pre-eclampsia in a second pregnancy in this group according to whether the first pregnancy had pre-eclampsia or not. The column percentages in Table 6 (giving the incidences of pre-eclampsia in a second pregnancy conditional upon the pre-eclampsia status of the first for the whole population) can be used to provide expected values for Table 10 and the corresponding value of χ^2, 8·03 with six degrees of freedom (two from each column) is not significant so we can conclude that the incidence of pre-eclampsia in the second pregnancy is dependent on the development of pre-eclampsia in the first pregnancy in essentially the same way as with women who did not change their civil status. The difference between our result and those of previous studies might, of course, be due to our indirect measure of change in partner; it might also be due to the fact that previous work on changed paternity has reported isolated cases or small studies, such as the series of 47 matched pairs reported by Feeney (1980) but, in contrast to our study, without any control for the stage of reproductive career.

If, then, we conclude that the earlier hypotheses were based on inadequate data or inadequate analysis where should we search for an aetiology of pre-eclampsia? One suggestion, prompted by the observed increase in HLA homozygosity in pre-eclampsia women, is that maternal recessive immune response genes contribute to the development of pre-eclampsia (Redman *et al.* 1978) and this hypothesis has been supported by Sutherland *et al.* (1981) who considered that the absence of, or a defect in, a single maternal recessive gene was consistent with their epidemiological data. Other factors that might influence the occurrence of pre-eclampsia have been proposed e.g. maternal nutrition, but the focus of this paper is on the potential alteration in the likelihood of proteinuric pre-eclampsia because of what might have happened in the previous pregnancy.

Our major findings are that proteinuric pre-eclampsia occurs in about one in 50 second pregnancies and there is no substantial protective effect (in the sense of this paper) due to the occurrence of a previous pregnancy, except that a previous normotensive singleton pregnancy ending in a livebirth at term lowers the incidence in the second pregnancy to about 1 in 140 and a previous pregnancy with proteinuric pre-eclampsia in conjunction with a low-birthweight baby increases the incidence in a second pregnancy to about 1 in 8. Our findings show that the *most* protection occurs among women who had a normotensive singleton livebirth at term in the first pregnancy. Any alteration to a suggested immunosuppressive response would have to be sought in the last weeks of normotensive pregnancy, that is among the vast majority of first pregnancies. The difference between a protection of 99·3% conferred by a normotensive as against 87·0% conferred by a proteinuric pre-eclampsia first pregnancy is of interest, but does not suggest that the investigation of immunosuppression will yield very useful results.

Alternatively, if proteinuric pre-eclampsia were a randomly occurring condition to which some might be genetically disposed, the interest is in finding particular subgroups where the incidence is very different from that in other subgroups. the findings of our study, that proteinuric pre-eclampsia is a condition of which the likelihood of recurrence in a subsequent pregnancy varies according to the gestation and birthweight in the first pregnancy, suggest the most fruitful avenue of investigation would be to concentrate the search for aetiology on those women who contracted proteinuric pre-eclampsia and who were delivered preterm, or who had a low-birthweight baby.

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Domperidone: secretion in breast milk and effect on puerperal prolactin levels

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Summary. The possible effect on the infant of dopamine antagonists used to promote lactation is cause for concern. Domperidone (Motilium) may be safer than other drugs in this group as it does not cross the blood–brain barrier. The mean serum level of prolactin 2 h after treatment with 20 mg of domperidone in the puerperium was 255 ng/ml compared with 150 ng/ml after a placebo. The mean domperidone level in all breast milk samples during treatment with 10 mg, three times daily, was 2·6 ng/ml. This was significantly more than levels after a single 20 mg dose sampled at 2 h (0·24 ng/ml) and at 4 h (1·1 ng/ml), and considerably less than values available for metoclopramide and sulpiride, relative to the therapeutic dosage. The effectiveness of domperidone to augment lactation requires further study.

Dopamine antagonists such as metoclopramide and sulpiride have been reported to improve lactation by raising serum prolactin levels (Sousa 1975; Guzmán *et al.* 1979; Lewis *et al.* 1980; Kauppila *et al.* 1981; Aono *et al.* 1979; Ylikorkala *et al.* 1982).

Of some concern is experimental evidence in rats which suggests that the first week of life is a vulnerable period for the functional maturation of central dopamine mechanisms (Engel & Lundborg 1982). Dopamine antagonists given to nursing rat mothers resulted in deficits of some dopamine-mediated responses in the offspring at 4 weeks of age. Of the clinical trials cited above, in only two were levels of metoclopramide (Lewis *et al.* 1980) and sulpiride (Aono *et al.* 1979) measured in breast milk. The estimated intake of metoclopramide was 130 μg/day assuming a milk intake of 1 litre/day and that of sulpiride was 1500 μg over the first 7 days assuming a total milk intake of 1500 ml.

In view of the possible sensitivity of immature central dopamine mechanisms to small amounts of dopamine antagonists, we have examined a structurally different dopamine antagonist, domperidone, whose primary action is peripheral rather than central. In the adult it does not cross the blood–brain barrier in any significant amount (Laduron & Leysen 1979). This may explain why it does not, in contrast to other dopamine antagonists, provoke extrapyramidal adverse effects (Reyntjens *et al.* 1978), and it may also be expected to cross less freely into breast milk. Its effect on prolactin secretion occurs at the pituitary level, outside the blood–brain barrier.

Domperidone has been shown to raise the serum prolactin level in non-lactating women from 8·1 to 110·9 ng/ml after one 20-mg dose while metoclopramide 20 mg raised the levels from 7·4 to 124·1 ng/ml (Brouwers *et al.* 1980).

The aims of this study were to document the effect of domperidone on prolactin levels in lactating women and to investigate the transfer of the drug into breast milk, with particular reference to possible shortcomings in the usual method of evaluating drug levels in breast milk.

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Subjects and methods

Ten mothers whose infants were temporarily unable to take breast milk agreed to take part in the study, which was authorized by the committee for research on human subjects of the University of the Witwatersrand. Six had been delivered by caesarean section, and four of the infants were premature, two were small-for-gestational age and one was postmature. The mean interval from delivery to commencement of the study was 4 days (range 2–8 days). On two successive days the subjects' breasts were expressed at 08.00 hours, two 10-mg domperidone or identical looking placebos were taken by mouth at 10.00 hours, blood was taken by venipuncture at 12.00 hours, and the breasts were emptied by manual expression at 12.00 hours (2-h specimen) and 14.00 hours (4-h specimen). The first treatment was with domperidone in five of the 10 subjects, and the sequence was double-blind in each case. The blood was separated by centrifugation and all serum and milk samples frozen at –20°C until assayed for prolactin (serum only) and domperidone levels. Prolactin levels were measured by radioimmunoassay at the South African Institute for Medical Research, and domperidone levels by radioimmunoassay (Huizing *et al.* 1980) at the laboratories of Janssen Pharmaceutica, Belgium.

The Wilcoxon signed ranks test (two-tail) was used to compare the serum prolactin levels after placebo and domperidone, and the milk domperidone levels in the 2- and 4-h samples in the study group. The *t*-test was used to compare the 2- and 4-h milk domperidone levels with previously reported mean levels for all milk specimens expressed during 4 days' treatment with domperidone, 10 mg 8-hourly, in the puerperium (Hofmeyr & van Iddekinge 1983).

Results

Prolactin levels

The mean serum prolactin level 2 h after treatment with 20 mg domperidone was 255 ng/ml compared with 150 ng/ml after placebo treatment in the same subjects on the preceding or subsequent day (Fig. 1), ($P<0{\cdot}05$).

Domperidone levels

In Table 1 the serum and milk domperidone levels after a single dose of domperidone are shown, and compared with levels in subjects on continuous domperidone therapy previously reported, as well as with reported levels for metoclopramide and sulpiride.

To determine whether drug levels in the early puerperium were relevant to use of the drug during subsequent lactation, domperidone levels were measured in breast milk expressed 2 h after the last dose in four subjects on continuous treatment with 10 mg 8-hourly after 1 to 3 months' lactation. The mean level of 2 3 ng/ml was similar to that of 2·6 ng/ml recorded on the same regimen in the early puerperium.

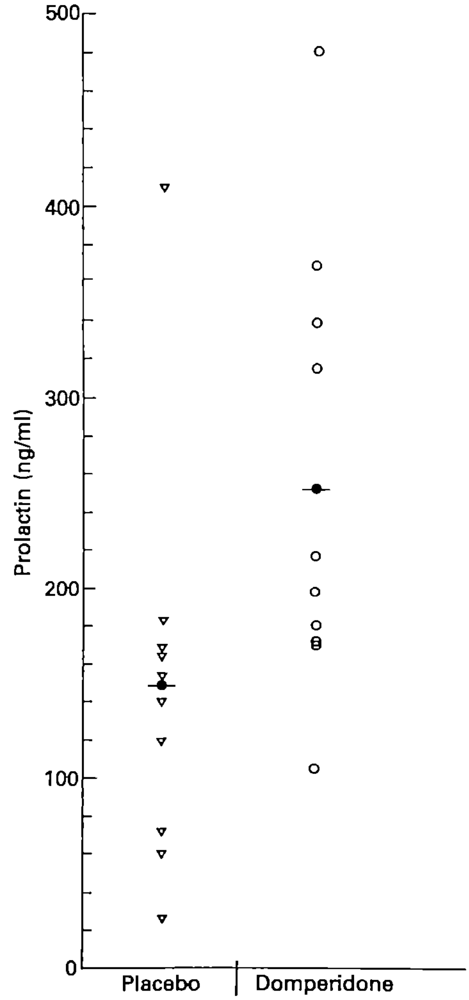

Fig. 1. Serum prolactin levels 2 h after treatment with placebo or domperidone. Horizontal bars represent the means.

Table 1. Comparison of dopamine antagonist levels in breast milk

Treatment	Serum		Milk			Milk : serum ratio
	Sampling (h)	Level (ng/ml)	Sampling (h)	Level (ng/ml)	Level per 10 mg of drug taken (ng/ml)	
Domperidone 20 mg single dose	2	8·0	2	$0{\cdot}24^{a}$	0·12	0·03
			4	$1{\cdot}1^{b}$	0·6	—
Domperidone 10 mg 8-hourly (Hofmeyr & van Iddekinge 1983)	1·75–3·0	10·3	All samples	$2{\cdot}6^{c}$	2·6	0·25
Metoclopromide 10 mg single dose (Lewis *et al.* 1980)	2	68·5	2	125·7	125·7	1·8
Sulpiride 50 mg twice daily (Aono *et al.* 1979)	—	—	2	970·0	194·0	—

a *vs* b: $P<0{\cdot}05$; b *vs* c: $P<0{\cdot}05$; a *vs* c: $P=0{\cdot}0001$.

Discussion

This study shows that there is a 70% mean increase in the already raised puerperal serum prolactin levels after a single dose of domperidone when compared with placebo. In common with other dopamine receptor antagonists, domperidone may therefore be effective in augmenting inadequate lactation. This effect requires further investigation.

It is of some importance that the usual method of measuring drug levels in breast milk 2 h after treatment with a single dose greatly underestimates the amount to which the infant would actually be exposed. Significantly higher breast milk levels were found 4 h after treatment, and significantly higher still on random sampling during continuous treatment with the drug. As secretion of milk takes several hours (Josimovich & Archer 1978) it is not surprising that sampling 2 and even 4 h after an individual dose should underestimate the overall secretion of the drug. This finding emphasizes the limited validity of studies of drug secretion in breast milk not based on sampling during continuous treatment with the drug in question (Giacoia & Catz 1979). Domperidone levels in breast milk were considerably lower than levels reported for metoclopramide or sulpiride relative to therapeutic dosage and in the case of metoclopramide, serum levels. The relatively high breast milk to serum ratio of metoclopramide is consistent with the known tendency for basic drugs to be selectively secreted in breast milk (Rasmussen 1958), and in the light of the above discussion may well have been underestimated in the study quoted (Lewis *et al.* 1980).

In addition to quantitative considerations, the potential for interference with maturation of central dopamine mechanisms should be less for domperidone than for other dopamine antagonists by virtue of its inability to cross the blood–brain barrier, particularly as recent evidence is contrary to the concept that the neonatal blood–brain barrier is ineffective (Saunders 1977).

Bonnar *et al.* (1975) have suggested the use of pharmacologically induced hyperprolactinaemia for contraception during breast-feeding. The very small amounts of domperidone appearing in breast milk may justify its investigation for this purpose.

The use of drug-induced hyperprolactinaemia to promote apparently inadequate lactation is controversial. Proper motivation and encouragement may be effective in most patients. There may be more justification for the use of drugs to induce lactation in unphysiological situations such as adoptive mothers who wish to breast-feed or for induction of lactation after complete cessation such as may occur during prolonged hospitalization of the infant. Whenever pharmacological augmentation of lactation is contemplated the possibility of adverse effects of the drug on the infant should be considered.

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Obstetric aspects of Gaucher disease

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Summary. The medical aspects of 21 pregnancies in 11 women with type I, non-neuronopathic Gaucher disease have been reviewed. One pregnancy ended in a spontaneous abortion at 12 weeks and two pregnancies in one patient resulted in two children with the Hurler syndrome which is unrelated to Gaucher disease. The other 18 pregnancies resulted in the birth of normal infants at full-term, four by caesarean section and the remainder by normal vaginal delivery. Only one patient experienced a significant exacerbation of her Gaucher disease during pregnancy. Fifteen of the pregnancies were associated with mild haematological complications but active intervention was necessary in only two instances. It can be concluded that there are few contraindications to pregnancy in women with Gaucher disease.

Type I non-neuronopathic Gaucher disease is an autosomal recessive metabolic disorder in which defective activity of acid beta-glucosidase leads to the accumulation of glucosylceramide in cells of the monocyte–macrophage system (Brady *et al.* 1965). Affected persons suffer chronic ill-health and complications secondary to involvement of spleen, liver and bone marrow (Frederickson & Sloan 1972).

There has been controversy concerning the reciprocal effects of Gaucher disease and pregnancy (Groen & Garrer 1948; Teton & Treadwell 1957; Bromberg *et al.* 1953; Greenwald & Fenton 1959; Hoja 1960). In an attempt to elucidate the problem we have reviewed the medical aspects of 21 pregnancies in 11 women with type I Gaucher disease.

Patients and methods

During the past decade we have investigated more than 50 persons with type I non-neuronopathic Gaucher disease. Eleven of these were women who had become pregnant and we have reappraised their obstetric histories for the purposes of this study. Their ethnic origins were: eight Ashkenazi-Jewish, one English and two Afrikaners. The clinical severity of their Gaucher disease was variable and the non-obstetric aspects of their condition have been presented and discussed in detail elsewhere (Goldblatt *et al.* 1978; Goldblatt & Beighton 1979*a, b*, 1982).

Obstetric findings

The obstetric histories of the 11 affected women are shown in Table 1. In general there was no clinical evidence of exacerbation of the Gaucher disease during pregnancy and nine of the 11 women completed 19 pregnancies without undue complications.

Eighteen of the pregnancies resulted in the birth of normal infants at full-term. Patient 2 had two children who have since been diagnosed as having the Hurler syndrome. This condition bears no pathogenetic relationship to the maternal Gaucher disease. Patient 4 had a spontaneous abortion at 12 weeks gestation but subsequently completed a normal, full-term pregnancy.

Patient 11 had a caesarean section for fetal

Table 1. Obstetric aspects of Gaucher disease

Patient	Pregnancy		Haematological status during pregnancy		Mode of delivery	Postpartum course
	Number	Duration	Clinical	Platelet count ($\times 10^9$/l)		
1	1	Term	Severe anaemia—required 3 units transfusion	140	NVD	Normal
	2	Term	Normal	150	NVD	Normal
2	1	Term	Mild anaemia+ thrombocytopenia	107	Forceps	PPH, conservative therapy
	2	Term	Mild anaemia+ thrombocytopenia	114	NVD	PPH, one unit blood
	3	Term	Mild anaemia+ thrombocytopenia	110	NVD	PPH, conservative therapy
	4	Term	Mild anaemia+ thrombocytopenia	108	NVD	PPH, conservative therapy
3	1	Term	Severe anaemia, multiple transfusions	145	NVD	Normal
4	1	Abortion	—	180	—	
	2	Term	Normal	170	NVD	Normal
5	1	Term	Thrombocytopenia	60	NVD	PPH, conservative therapy
	2	Term	Thrombocytopenia	68	NVD	PPH, conservative therapy
	3	Term	Thrombocytopenia	65	NVD	PPH, conservative therapy
6	1	Term	Mild anaemia	175	C/S for PET	Normal
7	1	Term	Normal	185	NVD	Normal
8	1	Term	Regular blood transfusions for anaemia	215	C/S for CPD	Normal
	2	Term	Regular blood transfusions for anaemia	190	C/S for CPD	Normal
9	1	Term	Normal	—	NVD	Normal
10	1	Term	Mild anaemia+ thrombocytopenia	79	NVD	Normal
	2	Term	Mild anaemia+ thrombocytopenia	85	NVD	Normal
	3	Term	Mild anaemia+ thrombocytopenia	75	NVD	Normal
11	1	Term	Normal	184	C/S for fetal distress	Died 3 weeks postpartum from ? overwhelming sepsis

NVD, normal vaginal delivery, PPH, post partum haemorrhage; C/S, caesarean section; CPD, cephalopelvic disproportion, PET, pre-eclampsia.

distress and had a pyrexial illness in the postpartum period. Despite prolonged management in the intensive care unit she died of an apparent septicaemia 3 weeks after delivery. It is of interest that she had had a splenectomy 5 years previously and that she maintained satisfactory blood counts throughout her pregnancy. Two other patients were delivered by caesarean section, one (no. 6) because of pre-eclampsia and the other (no. 8) for cephalopelvic disproportion. All the other pregnancies ended in a normal vaginal delivery.

Haematological problems during the pregnancies were not severe and were easily controlled in the majority of instances. Seven of the 11 patients had some degree of anaemia before and during pregnancy, but only two required blood transfusions. Seven of the 21 pregnancies were associated with postpartum haemorrhages, all seven occurred in two patients (nos 2 and 5) who both had chronic thrombocytopenia. The exact aetiologies were not documented on each occasion and in most instances they were managed satisfactorily by conservative measures, only once was a blood transfusion necessary (patient 2).

Several of the patients experienced a sense of well-being during pregnancy and the postpartum period. There was considerable improvement in the general condition of patient 1 who had two normal pregnancies and vaginal deliveries despite severe musculoskeletal complications which had confined her to a wheelchair for 5 years preceding the pregnancy. Patient 3 was an exception, as she experienced an acute exacerbation of orthopaedic and haematological complications during the course of her pregnancy. Her general condition improved again after delivery.

Lactation was consistently normal and, apart from the problems mentioned above, the puerperium was generally uneventful.

Discussion

There has been considerable controversy concerning the reciprocal effects of Gaucher disease and pregnancy. For a long time these were considered to be incompatible and pregnancy was strongly discouraged in patients with Gaucher disease. It was thought that pregnancy endangered the patient's life as well as presenting a risk of transmission of the condition to the unborn child. For these reasons therapeutic abortion was sometimes advocated (Groen & Garrer 1948; Bromberg *et al.* 1953).

Teton & Treadwell (1957) suggested that there was an increased incidence of sterility, spontaneous abortion and neonatal death in affected individuals, but extensive reviews of the literature (Bromberg *et al.* 1953; Greenwald & Fenton 1959; Hoja 1960) contradict this viewpoint. A number of successful pregnancies have been reported (Elliott 1952; Logan 1953; Addleman & Gold 1963; Mendel & McCullough 1968; Houlton & Jackson 1978). These investigators all agreed on the need for a change of attitude regarding the advisability of pregnancy in the patient with Gaucher disease and emphasized that pregnancy should not be discouraged because of fear of complications.

Contemporary understanding of the mechanism of autosomal recessive inheritance of Gaucher disease, together with modern prenatal diagnostic and screening procedures, enables prediction of the status of the unborn child. For this reason the potential risk of transmission of the genetic disorder to future offspring no longer enters into the debate and it would be appropriate for these patients to be counselled to allay doubts and be reassured about their prospects of having normal children.

It is now clear that there is no evidence to indicate that pregnancy significantly affects the course and prognosis of Gaucher disease in any adverse way. Bromberg *et al.* (1953) described a subjective feeling of increased well-being experienced by pregnant patients and our study confirms this impression. This phenomenon has been reported in many conditions (Persellin & Rutstein 1979) and is especially well documented in rheumatoid arthritis (Persellin 1976). However, the postpartum deterioration which often occurs in patients with rheumatoid arthritis has not been found in Gaucher disease.

Pregnancy does not seem to have adverse effects on the spleen and liver in Gaucher disease and in our series, the enlarging uterus did not cause mechanical embarassment to these organs. Equally, the spleen and liver did not enlarge during pregnancy. Splenic rupture has never been reported during the stress of parturition in patients with Gaucher disease and there is no evidence that the metabolic demands of pregnancy cause liver damage. It is generally accepted that the hazards of rupture of the uterus or obstruction to labour due to progressive splenomegaly do not justify termination (Teton & Treadwell 1957). The potential haematological complications of Gaucher disease may require special intrapartum management, but they have little overall influence on the outcome of the pregnancy. The majority of affected individuals have a chronic low-grade anaemia which may be augmented by the secondary anaemia of pregnancy. This problem is usually controlled with haematinics and rarely may necessitate the use of blood transfusion. There is sometimes a minimal increase in the bleeding diathesis during pregnancy, labour and the postpartum period. The haemorrhagic propensity in Gaucher disease is primarily related to the severity of the thrombocytopenia and possibly, to ill-defined defects in coagulation factors (Sawitsky & Noklan 1972). There has been only a single report of uncontrolled postpartum haemorrhage resulting in the patient's death (Groen & Garrer 1948) and in this instance the exact aetiology of the protracted haemorrhage was not discovered. It is advisable that individuals who are significantly thrombocytopenic should be carefully monitored during labour with cross-matched blood on standby. Platelet infusions are generally of no therapeutic value as the enlarged spleen rapidly consumes the administered platelets.

The size of the spleen alone is not an indication for antepartum splenectomy and the operation should only be performed for the standard haematological indications which have been discussed in detail by Rose *et al.* (1982). If splenectomy is undertaken, the second trimester is the optimal time because there is the least danger of abortion or premature labour in this phase of pregancy (Decker & McWhorter 1956; Hoja 1960; Watov & Sandre 1964).

Hoja (1960) advocated the use of steroid therapy as a temporary measure before splenectomy to induce remission in selected pregnant women with Gaucher disease. He also suggested that pregnancy should be discouraged when pancytopenia and bleeding problems recur due to Gaucher marrow infiltration following splenectomy. This problem arose with patient 3 in our study and she was counselled against having further pregnancies for these haematological reasons.

The spleen appears to have no mechanical effect on the enlarging uterus and early reports of an increased frequency of spontaneous abortions due to splenomegaly have been thoroughly disproved. There is also no evidence for decreased fertility in men or women with Gaucher disease. Furthermore, the fetus develops normally *in utero* and the infant experiences no specific neonatal problems as a consequence of maternal Gaucher disease.

Theoretically, severe osseous complications with resultant deformity of the hip joints and pelvic bones could affect labour through distortion of the skeletal components of the birth canal, but obstruction to normal vaginal delivery is very unusual in affected women. Despite significant orthopaedic complications in some of our patients caesarean section for cephalopelvic disproportion was required in only one patient.

We consider that the appropriate response to enquiries from a patient with Gaucher disease regarding the desirability of pregnancy should be made on a basis of optimism and encouragement. Our experience accords with published reports that women with Gaucher disease tolerate pregnancy well and show no increased incidence of sterility, abortion or stillbirth.

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The impact of screening on the incidence of cervical cancer in England and Wales

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Summary. Age-specific incidence curves for clinical cancer of the cervix in England and Wales show progressive changes over the period 1963–1978; in particular, a large reduction in incidence is seen in the age group 35–54. Since screening on any scale began in the early 1960s, we have investigated how much of this reduction in incidence in the middle age range can be attributed to detection of pre-invasive disease. Data on registrations of in-situ cancer have been used to estimate the patterns that might have been observed in the absence of screening. The results indicate clear cohort effects on incidence, with rising rates in the generations born 1906–1921 and since 1931, with a fall in the decade between. In addition to this, screening has probably led to a substantial reduction in the number of cases of clinical cancer in women aged 35–54, but has had little effect over the age of 60 where virtually no screening has been performed. Below age 35 the observed increase in incidence may be considerably less than it would have been in the absence of screening.

It has become evident that the steady decline in all-ages mortality from cancer of the cervix in England and Wales conceals rising mortality rates for women under 35 years of age (Yule 1978; Roberts 1982). Hill & Adelstein (1967) studied cohort rates of mortality for the years 1950–1965, and a more recent analysis (OPCS 1981*a*) confirms and extends their findings; mortality rates at all ages have clearly fallen for women born between 1926 and 1936, but have risen in each successive generation since then. These changes in mortality rates have been accompanied by similar changes in the incidence rates of clinical carcinoma of the cervix (Draper & Cook 1983).

In this paper we examine trends in cancer incidence and try to assess how much of the changes observed can be ascribed to mass screening activities. This analysis is comparable to that performed on data from the five Nordic countries (Hakama 1982), where different intensities of mass screening were clearly reflected in the time trends in incidence. In addition we have attempted to quantify the impact of cervical cytology, by estimating what the incidence might have been if there had been no screening activity, using data on the number of cases of carcinoma *in situ* detected annually. We confine our analysis to incidence since the interpretation of time trends in mortality is complicated by secular changes in survival rates.

Subjects and methods

The number of registered cases of clinical cancer of the cervix and of carcinoma *in situ*, by 5-year age groups, were obtained for the years 1962–1978 from the Supplements on Cancer of the Registrar General's Statistical Review (for 1962–1970), and from the Office of Population Censuses and Surveys (OPCS; Cancer Statistics: Registrations) for 1971–1978. For the years 1962–1964 carcinoma *in situ* of the uterus was registered as 'uterus (premalignant)'; these have been taken to equate to in-situ lesions of the cervix. Population estimates by 5-year age groups are available from the Registrar General's Statistical Reviews, and OPCS Population

Estimates, so that incidence rates for 5-year age groups can be calculated.

In order to investigate the effect of screening for cervical cancer, and in particular to estimate what the incidence rates *might* have been in the absence of screening, a method of adding some of the in-situ cases to clinical cases, with an appropriate time lag, was devised. The number of clinical and in-situ cases at individual years of age were estimated from the 5-year age groups using quadratic interpolation; a specified proportion of in-situ cases could then be added to clinical cancers after a defined interval by single year of age. The appropriate proportion of in-situ cases to be added to the clinical cancers is determined first, by the proportions of lesions that regress and second, by the distribution of the lead-times of those that do not. In the simplest formulation of natural history we supposed that the time to clinical surfacing of the in-situ cases progressing to invasive cancer was evenly distributed over 16 years of observation. This would be the case if the sojourn time in the in-situ phase was exactly 16 years, and the registered cases represented a random sample of all prevalent in-situ lesions in the population. This natural history was used, assuming either that half of the detected lesions would have progressed in a 16-year period (natural history A) or that all of them would have done so (natural history B). Under assumption A, therefore, we added 1/32 of the in-situ cases to the clinical cancers in each successive year at each successive (single year) age group (eg, suppose 32 in-situ cases were estimated to occur at age 37 in 1970; then one case is added to clinical cancers at age 38 in 1971, one at age 39 in 1972, and so on). Summing for each 5 years allows calculation of the resulting age-specific rates.

As an extreme alternative to this natural history, we assumed a distribution of sojourn times which was exponential in form, so that a random sample of cases would yield lesions whose distribution of lead times was also exponential (Day & Walter 1984). We tested two such distributions, one (C) with a median of 16 years (exponential parameter —0 0433) and a second (D) more skew distribution with an exponential parameter of —0·1 and a median of 6·9 years. Both distributions are truncated at 16 years (the maximum follow-up in our data) and distribution D scaled down by a factor of 0·63 to give 50% progression in 16 years, similar to distributions A and C.

The analysis of time trends for carcinoma of the cervix is complicated by changing patterns of hysterectomy, so that the proportion of women in each age group who are not at risk of cervical cancer (having had a hysterectomy for other reasons) does not remain constant. Using data from the Hospital In-Patient Enquiry (HIPE), Alderson & Donnan (1978) estimated the cumulative percentage of women who had had a hysterectomy, by age, up to 1975. Using their values and hysterectomy rates for 1976–1978 calculated from HIPE data on numbers of operations by age, diagnosis and type of operation, we estimated the prevalence of hysterectomy by age up to 1978.

Results

Fig. 1 shows the age-specific incidence rates of clinical carcinoma of cervix for the four different years 1963, 1968, 1973 and 1978. There is an interesting change in the incidence curve over the 15-year period encompassed. In 1963 the incidence curve is unimodal with a peak incidence at age 45–49. Thereafter there appears to be a progressive flattening of the curve in the age range 35–49 until by 1978, it is distinctly bimodal, with peaks at 35–39 and 55–59. The decrease in the 40–49 age-group is nearly 50%.

The denominators of the curves shown are expressed as 'uteri at risk'. Table 1 shows the proportion of hysterectomized women by age at the different periods shown, estimated as described above. Maximum prevalence of hysterectomy is about 12% in the age group 50–59 by 1978. The conventional incidence rates (per 10^5 women) will be lower than those shown by a factor of $1-h$, where h is the age-specific proportion of women without a uterus for the year in question.

Fig. 2 shows the same data as Fig. 1, but the incidence rates have been drawn for separate birth cohorts. These curves show a moderate rise in incidence rates for the cohorts born between 1906 and 1916, a rather indistinct maximum for the 1916 and 1921 cohorts, and then a dramatic fall in incidence between the 1921 and 1931 cohorts. Minimum rates are seen in the 1936 cohort, after which they rise again.

Screening was introduced in England and Wales in the early 1960s; by 1965 about 700 000 smears were being examined annually, and in 1980 the number of tests had reached 2 928 000 (Roberts 1982). This increase in activity is reflected in the number of in-situ cancers

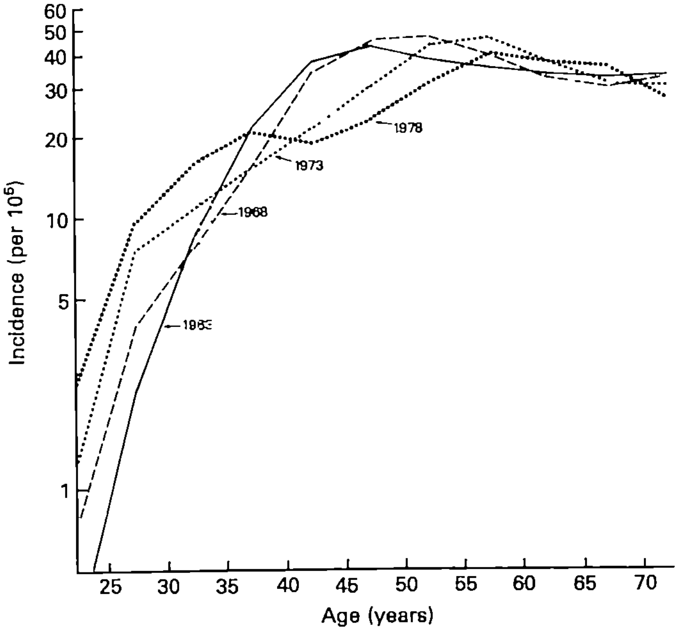

Fig. 1. Observed incidence of clinical cancer of the cervix in 1963, 1968, 1973 and 1978.

registered (Table 2), which has been increasing since the mid 1960s especially in the age range 25–44; that is, it has affected the birth cohorts of women born since about 1921. Since it is in these cohorts that the dramatic changes in incidence of clinical disease have occurred (Fig. 2), we have investigated the consequence of supposing that a proportion of the in-situ cancers would have surfaced later as clinical cancer.

The duration of the in-situ phase appears in general to be long, with a mean duration of 8–10 years or more (Dunn & Martin 1967; Fidler *et al.* 1968) and there is increasing evidence that not all in-situ lesions will ever progress to the invasive clinical state (Boyes *et al.* 1982). However, little is known about the precise natural history, in terms of the percentage of lesions which regress, and the distribution of sojourn times in the in-situ phase. In our simplest model of natural history (A) we assumed that of the carcinoma in-situ cases diagnosed each year, 1/32 would have advanced to clinical cancer in each of the 16 subsequent years. Since we are only analysing data from a 16-year period, we do not need to make any assumption about progression taking longer than 16 years. The incidence rates of clinical cancer were modified by the addition of in-situ cases in this manner, and Fig. 3 gives the resulting cohort curves. The differences between cohorts born 1906 to 1936 are much less marked than in Fig. 2, with successive cohorts up to that of 1921 showing slight increases, followed by a fall to the 1931 cohort. After 1936, however, the increase appears even sharper than that seen in the unmodified data. The corresponding cross-sectional curves (Fig. 4) show rather larger differences between the different periods at young ages (under 35), but much less of a reduction in incidence in the 35–54 age-group.

Table 1. Estimated proportion of women with hysterectomy, by age-group (England and Wales)

Age (years)	1963	1968	1973	1978
25–29	0 000	0·001	0 002	0·003
30–34	0·002	0·005	0 009	0 013
35–39	0 013	0·017	0·026	0 033
40–44	0 030	0 045	0·054	0·064
45–49	0·049	0 068	0 089	0 096
50–54	0 056	0 078	0 101	0·122
55–59	0 056	0 069	0·094	0 117
60–64	0 056	0 064	0·077	0 101
65–69	0 058	0 064	0 071	0·084
70–74	0·058	0·066	0·072	0 080
75–79	0 055	0 064	0 071	0 078

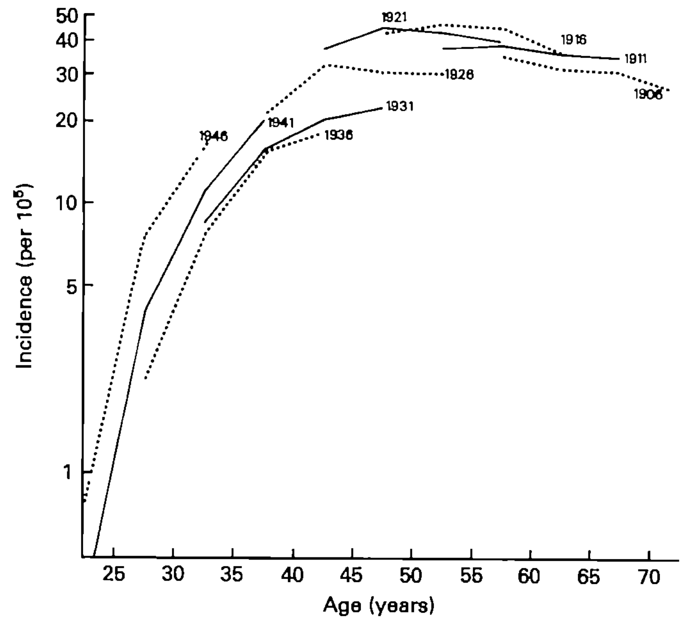

Fig. 2. Observed incidence of clinical cancer of the cervix in successive birth cohorts.

Our thesis is that Fig. 3 displays the type of behaviour seen in the absence of mass screening, whereas the unusual patterns of Fig. 1, shown in alternative fashion in Fig. 2, have resulted in large part from screening activities. The cohort curves in Fig. 3 appear more regular than those in Fig. 2—they are more clearly parallel, and show more plausible cohort differences in terms of underlying trends in the occurrence of disease. In addition, the cohort curves of Fig. 2 flatten out earlier than those of Fig. 3, and the 1926 cohort curve actually decreases after age 40. This behaviour is similar to that seen in Sweden and Denmark (Hakama 1982) the Scandinavian countries where mass screening appears to have had a moderate overall effect on incidence. By contrast the cohort curves in Fig. 3 resemble those from Norway, where there has been relatively little organized mass screening. The comparison of the curves from Figs. 2 and 3, together with the curves from Norway, are shown in Fig. 5. The adjusted rates from England and Wales are almost parallel to the Norwegian rates, whereas the observed rates from England and Wales diverge substantially.

The total number of clinical cancers actually observed between the ages of 15 and 84 in the period 1962–1979 was 69 620; with natural history A the number 'expected' in the absence of screening was estimated to be 77 190. With the non-regressive natural history (B) this expected number is considerably higher (84 760), so that the cohort curves of Fig. 3, although they remain parallel, are higher, and the maximum rate is seen at age 55–60 in the 1921 cohort (57·7 per 10^5). With natural histories C and D (exponentially distributed lead times) the in-situ cases are deemed to have become clinical cancer earlier than with history A. The total 'expected' cancers at ages 15–84 are 78 322 and 79 367 respectively. Rates observed at (or soon after) the ages subjected to

Table 2. Average annual number of registrations of carcinoma *in situ* of the cervix (England and Wales)

Age group	1962–1965	1966–1970	1971–1975	1976–1978
15–24	15	103	193	306
25–34	142	679	1049	1843
35–44	313	973	769	1056
45–54	178	624	456	423
55–64	50	138	138	150
65–74	24	42	43	56
≥75	8	11	11	12
All ages	730	2570	2659	3846

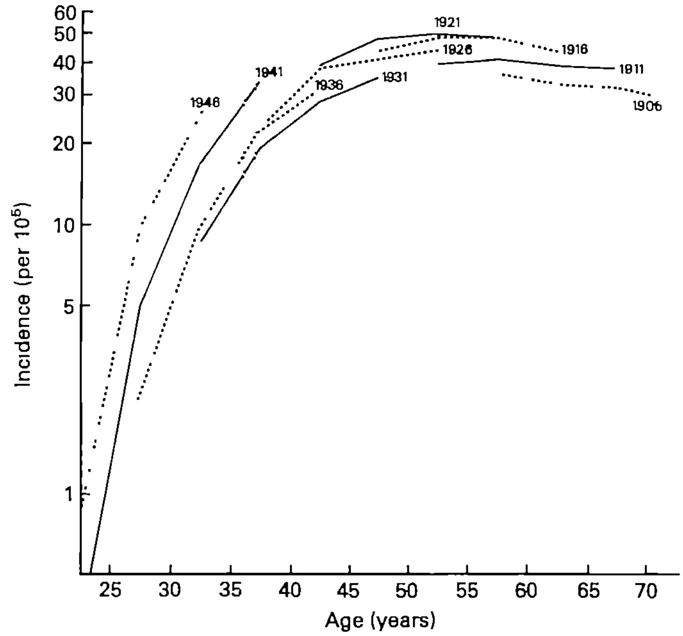

Fig. 3. Incidence of cervical cancer in birth cohorts after addition of in-situ cases (natural history A: see text).

screening (i.e. 30–49) are rather higher than with history A, so that the curves for the 1921–1936 cohorts appear rather more flexed than in Fig. 3, but otherwise the general pattern is unchanged.

The observed pattern of cervical cancer incidence, Figs 1 and 2, seems therefore to be a combination of differences in the underlying risk of disease between different cohorts (a rise until 1921, a fall to 1931, and a steady increase since then), together with the results of screening which have affected clinical cancer incidence in cohorts born subsequent to 1921, especially those born between 1926 and 1941, where there are the greatest changes between the curves of Figs 2 and 3.

In Table 3 we present the number of clinical cancers observed during 1 year, 1978, and compare these with the numbers estimated with the natural histories of in-situ disease A–D described above. The number of cancers 'prevented' is obviously directly proportional to the rate of progression, so that the figures in column B (100% progression) are double those in column A (50% progression). However, within the range of plausible lead-time distributions (A, C and D), the total saving varies little. Natural histories which give a short lead time to a higher proportion of in-situ cases (the exponential distributions C and D) do, however, lead to the avoidance of clinical cancer at younger ages (where the intensity of screening is highest).

Discussion

The existence of a National Cancer Registry in England and Wales has allowed calculation of incidence rates for the whole country since 1962. The functioning of the system has been reviewed recently (OPCS 1981*b*). It is clear that there is a degree of underascertainment of cancer cases in some regions, but for the study of time trends in incidence, this should be of relatively little importance. It is possible that registration has improved over the period covered in this study; however, this would be unable to explain the patterns and trends in incidence observed, unless it were postulated that the degree of ascertainment was changing in a different fashion for women of different birth cohorts. It seems intuitively probable that carcinoma in-situ, being a relatively trivial lesion, would be more under-registered than clinical cancer. Some independent evidence on the occurrence of carcinoma *in situ* is available from the results of biopsy following the

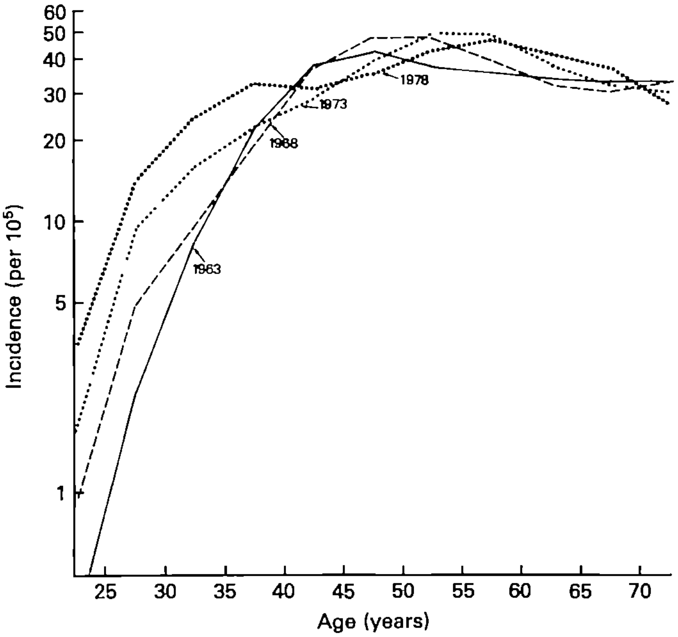

Fig. 4. Incidence of cervical cancer in 1963, 1968, 1973 and 1978, after addition of in-situ cases (natural history A: see text).

finding of a positive smear (Roberts 1982), and this suggests that about 65–70% of in-situ cases are registered (although estimates based on biopsies may be high due to duplicate specimens from the same patient). We have made no allowance for dysplastic lesions of the cervix, which appear to be detected and biopsied about 30–40% as often as carcinoma *in situ* (Roberts 1982). The majority of dysplasias regress to normality, and those that do not would take many years to reach the stage of invasive cancer (Hulka & Redmond 1971; Nasiell *et al.* 1976); in any case during the years of this analysis many dysplasias would have been followed up untreated until carcinoma *in situ* developed (and was registered as such). Nevertheless, the addition of half the registered in-situ cases in Figs 3 and 4 may be conservative, so that the fall in incidence in the 1921–1931 cohorts may be an overestimate and the subsequent rise an underestimate of the true position.

Relatively little is known about the natural history of cervical cancer in quantitative terms, and although we have examined four rather extreme possibilities, the model of lead-time distributions which was used is still a simplistic one. No account has been taken, for example, of the possible variations with age of lead-time durations, or regression rates. Moreover, towards the end of the period studied, some of the in-situ lesions detected would have been in previously screened women, so that lead times would be longer than in unscreened populations. The effect of this latter bias may, however, be small, since it was estimated that in 1979 up to 40% of smears were first tests (Draper & Cook 1983). Because of the difficulty of quantifying such factors we have not attempted to incorporate them into a more complex model. The results obtained using three very different lead-time distributions are quite similar, and the coherence of the calculated rates which result from the approach described suggests that they may be a reasonable approximation to the truth.

Ashley (1966) postulated two forms of cervical carcinoma, partly because of inflexions noted in the curve of age specific mortality rates. Hakama & Penttinen (1981), noting bimodality in the age-specific incidence curve for Finland, came to the same conclusion, and derived theoretical component curves to fit the data. It is clear that no such explanation need to be sought for the England and Wales data presented here. The existence of bimodality is the result of underlying

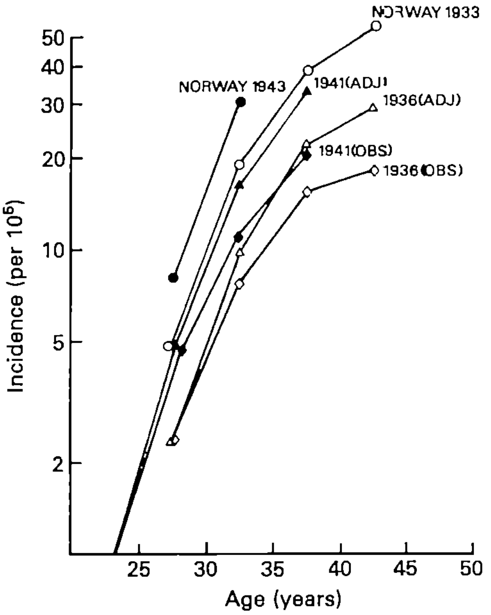

Fig. 5. Comparison of observed and theoretical cohort curves from England and Wales with those seen in Norway. OBS, rates of invasive cervix cancer observed in England and Wales; ADJ, rates adjusted by the addition of in-situ cases (natural history A: see text).

trends in disease incidence in different cohorts, and the removal of precursor lesions (carcinoma *in situ*) in younger women (aged 25–44) since the mid 1960s. Cancer incidence curves for the Nordic countries where screening has been widespread (Denmark, Sweden) show the same effects.

It is interesting to speculate on the causes of the pattern observed in the set of theoretical curves depicting what might have happened in the absence of screening (Fig. 3). Adelstein *et al.* (1971) noted that cohort mortality rates for cervical cancer in several countries appear to be maximum for those generations of women who were in their late teens and early twenties during periods of social instability (wartime). The present data seem to confirm this for the period of the second war. In addition, however, there seems to be a rapidly increasing risk starting with generations born in 1931 in keeping with that seen in mortality data (Draper & Cook 1983). It may be that this rise is due to changing sexual mores, increasing cigarette smoking (Clarke *et al.* 1982) and the use of oral contraceptives (Vessey *et al.* 1983) in preference to barrier methods of contraception which may offer a degree of protection (Wright *et al.* 1978).

The estimates presented suggest that the screening programme in operation in England and Wales has had a substantial effect on cervical cancer incidence, mainly in women below the age of 60, and has partly hidden the large rise in incidence in young women under 35. The actual numbers of cancers that are being prevented by the screening programme will depend upon the precise natural history of carcinoma *in situ*. Table 3 indicates the range of possibilities for the numbers of cases of cervical cancer which might

Table 3. Number of cases of invasive cervical cancer observed in 1978, and the number that might have been expected in the absence of screening

Age (years)	Observed	'Expected'				Number 'prevented'				Percentage 'prevented'			
		A	B	C	D	A	B	C	D	A	B	C	D
20–24	45	57	70	61	66	12	25	16	21	21	36	26	32
25–29	163	241	319	261	285	78	156	98	122	32	49	38	43
30–34	282	438	593	470	504	156	311	188	222	36	52	40	44
35–39	281	458	635	483	505	177	354	202	224	39	56	42	44
40–44	233	393	554	406	413	160	321	173	180	41	58	43	44
45–49	292	441	590	445	442	149	298	153	150	34	51	34	34
50–54	399	553	707	551	541	154	308	152	142	28	44	28	26
55–59	549	673	796	669	657	124	247	120	108	18	31	18	16
60–64	454	518	581	515	508	64	127	61	51	12	22	12	10
65–69	441	474	506	473	470	33	65	32	29	7	13	7	6
70–74	290	306	322	306	305	16	32	16	15	5	10	5	5
75–79	213	222	232	222	221	9	19	9	8	4	8	4	4
≥80	229	238	247	237	236	9	18	8	7	4	7	3	3
Total	3871	5012	6152	5099	5133	1141	2281	1228	1279	23	37	24	25

A–D represent the different natural histories referred to in the text.

have occurred in 1978 in the absence of screening; the maximum reduction is seen in the younger age groups (under 55), with relatively little effect amongst the elderly.

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Complications of cone biopsy related to the dimensions of the cone and the influence of prior colposcopic assessment

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Summary. A retrospective study of the complications of cone biopsy showed that among 915 women examined between the years 1976 and 1982, 121 (13%) had primary or secondary haemorrhage, 153 (17%) cervical stenosis and 39 (4%) subsequent infertility or an abnormal pregnancy. Cervical stenosis was commonest among women who had had long cones removed. Stenosis occurred more often in the group of women who had been assessed by colposcopy before operation but this was due to the fact that prior colposcopy selected a favourable group of patients with lesions of limited extent that were susceptible to treatment by local destructive therapy, so that prior colposcopic assessment resulted in the removal of longer cones.

Removal of a cervical cone has for long been an accepted technique for both diagnosis and treatment of cervical intraepithelial neoplasia (CIN) (McLaren 1967) but in recent years the use of colposcopy to assess the transformation zone has allowed some patients with this disease to be treated by local destructive techniques such as the carbon dioxide laser, electrodiathermy, cold coagulation or cyrocautery. Cone biopsy remains necessary if the whole of the transformation zone and particularly its upper limit cannot be visualized on colposcopy, if invasive disease is suspected or if cytological findings are not explained after full assessment which has included examination of a directed punch specimen. But, as reported by many workers (McCann *et al.* 1969; Claman & Lee 1974; Schulman & Ferguson 1962; Hollyock & Chanon 1972; Byrne 1966; Villasanta & Durkan 1966; Davis *et al.* 1972; Leiman *et al.* 1980), removal of a cone may be complicated by haemorrhage, stenosis or infertility.

The present study was designed to investigate the occurrence of complications of conization in women treated at the Birmingham and Midland Hospital for Women, and to assess the effects of cone size and of prior colposcopic investigation.

Patients and methods

During the years 1976–1982, 975 patients underwent conization at the Birmingham and Midland Hospital for Women and this study is based on 915 of these for whom full records were accessible. The patients fall into one of two groups, a large group of 684 women who had attended the colposcopy clinics under the care of two of us (J.A.J. and J.M.E.) and had thus been exam-

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ined colposcopically before and after operation, and a smaller group of 231 women who were admitted under H.O.N. and had not been colposcoped.

A standard proforma was used to record demographic data, details of pre-operative assessment and immediate or delayed complications. Histopathology reports were reviewed for all specimens; 788 gave details of the maximum width and anteroposterior dimensions of the epithelium covered base of the cone and its total length, measured to the nearest millimetre after fixation in formal saline.

All statistical analyses were performed using a χ^2 test with Yates' correction.

Results

Complications

While these can be classified into early or late according to the time at which they occur, the most important early complication was haemorrhage due to surgical trauma, and the most important late complication was cervical stenosis due to healing and fibrosis and our analysis has given greatest attention to these (Table 1). Cervical stenosis is of particular importance because of the difficulty caused in follow-up examination, both cytological and colposcopic, but it may also give rise to symptoms; amenorrhoea and dysmenorrhoea are discussed below but infertility and problems in any later pregnancy also occur. These are listed in Table 1 but are not discussed further.

Haemorrhage. All patients in whom postoperative haemorrhage was severe enough to need further treatment have been included. Haemorrhage can be subdivided into that occurring within 24 h of operation and that occurring later. In this series primary haemorrhage occurred in 52 (6%), and secondary in 69 (7%); no haemorrhage occurred later than 12 days after operation. Table 2 shows that 30 patients were treated by blood transfusion only but 82 needed resuturing or repacking under general anaesthesia and nine others required an immediate hysterectomy.

Cervical stenosis. In 153 patients (17%) cervical stenosis was found on follow-up examination and 76 of them complained of symptoms attributable to stenosis which necessitated further operative treatment; 12 had amenorrhoea shown to be due to haematometra and 64 dysmenorrhoea. Of the 76 patients with such symptoms 31 had a hysterectomy and the other 45 had a cervical dilatation under general anaesthesia. Seventy-five patients were asymptomatic, stenosis being found on simple inspection or colposcopy; the use of the colposcope in follow-up examination, with its emphasis on the need to identify the postoperative squamocolumnar junction, increases awareness of degrees of stenosis not great enough to cause symptoms. Fig. 1 illustrates the frequency of stenosis, both symptomatic and asymptomatic, for each year of the study and shows an increase in asymptomatic stenosis.

Table 1. Complications of cone biopsy in 915 patients

Complication	Number	%
Haemorrhage	121 (101)	13·2 (12·8)
Primary	52 (46)	
Secondary	69 (55)	
Cervical stenosis	153 (138)	16·7 (17·5)
*Infertility	32 (27)	3·5
**Pregnancy complications	7 (6)	0 8

Number in brackets denotes cases where cone dimensions recorded, $n = 788$.

*Referred as failure to conceive after 12 months unprotected intercourse.

**Three mid-trimester abortions ascribed to cervical incompetence. Four cervical dystocia ascribed to post conization fibrosis.

Effects of cone biopsy dimensions on complications

The length and base measurements of the cone specimens were available for analysis in 788 cases (86%). The distribution of lengths of the

Table 2. Cone biopsy complications

Complication	Management	*n*
Haemorrhage	Immediate hysterectomy	9
	Re-suture/re-pack under general anaesthesia	82
	Blood transfusion only	30
	Total	121
Cervical stenosis	Hysterectomy	31
	Cervical dilatation	45
	No treatment	77
	Total	153

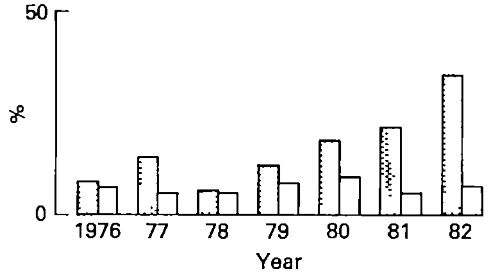

Fig. 1. The incidence of stenosis both symptomatic (□) and asymptomatic (□) after each year of the study.

cone biopsies is presented in Fig. 2. The mean length was 24.7 mm. Cone biopsies of ≤25 mm have been classified as short cones ($n = 462$), those >25 mm ($n = 326$) as long. Cone biopsies with a maximum base dimension of ≤25 mm ($n = 466$) were defined as narrow cones and those >25 mm ($n = 322$) as broad.

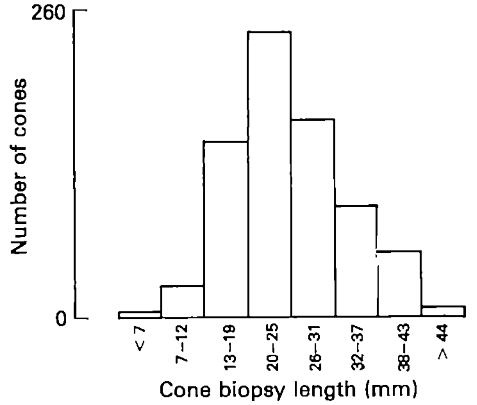

Fig. 2. The distribution of lengths of cone biopsy

Haemorrhage. This occurred in 101 patients of the 788 for whom cone biopsy dimensions had been recorded. In 46 patients haemorrhage occurred at or within 24 h of surgery. In the remaining 55 patients haemorrhage occurred after 24 h and up to 12 days after conization. The number of patients with primary and secondary haemorrhage, as well as the measures taken to manage these complications, are compared for long and short cones, and narrow and broad cones in Table 3. The increase in primary haemorrhage occurring after broad cone biopsies as compared to that occurring after narrow cone biopsies just reached statistical significance ($0{\cdot}02 > P > 0{\cdot}01$). No other significant differences were seen when long and short cones and broad and narrow cones were compared.

Cervical stenosis. The occurrence of cervical stenosis and of symptomatic cervical stenosis (dysmenorrhoea, amenorrhoea) is analysed in Table 4 with respect to cone length and base dimensions. There was a highly significant ($P < 0{\cdot}001$) association between long cones and cervical stenosis. To assess whether this effect was related to base dimensions, the two variables have been analysed together in Table 5. This demonstrates that the effect is due to length alone. In Table 6 the effect of patients' age and parity on stenosis is considered. Cone length, again, is a significant factor but no direct effect of age or parity is seen. Relatively more long cones were removed from multiparous patients and from those over 35 years of age (including nullipara).

Colposcopic assessment

Of the 915 patients in the study 684 (75%) had a

Table 3. Effect of cone biopsy dimensions on haemorrhage

Cone dimension	Number	Primary haemorrhage	Secondary haemorrhage	Required immediate hysterectomy	Required re-suture re-packing	Required transfusion
Length						
≤25 mm (short)	462	22	29	5	38	11
>25 mm (long)	326	24	26	4	28	18
		$0{\cdot}5>P>0{\cdot}1$	$0{\cdot}5>P>0{\cdot}1$	$P>0{\cdot}5$	$P>0{\cdot}5$	$0{\cdot}05>P>0{\cdot}02$
Maximum base dimension						
≤25 mm (narrow)	466	19	30	5	32	13
>25 mm (broad)	322	27	25	4	34	16
		$0{\cdot}02>P>0{\cdot}01$	$P>0{\cdot}5$	$P>0{\cdot}5$	$0{\cdot}1>P>0{\cdot}05$	$0{\cdot}5>P>0{\cdot}1$

Table 4. Effect of cone biopsy dimensions on cervical stenosis

Cone dimension	Number	Number stenosed	Number c/o dysmenorrhoea
Length			
≤25 mm (short)	462	59 (12·8%)	26 (5·6%)
>25 mm (long)	326	79 (24·2%)*	29 (8·8%)
		0·001>*P*	0·5>*P*>0·1*
Maximum base dimension			
≤25 mm (narrow)	466	83 (17·8%)	27 (5·7%)
>25 mm (broad)	322	55 (17·1%)*	28 (8·7%)
		P>0·5*	0·5>*P*>0·1*

*Not significant.

Table 5. Effect of base dimensions and length of cervical stenosis

Length	Base dimensions			
	<25 mm (narrow)	>25 mm (broad)	Total	
≤25 mm (short)				
Number stenosed	45	14	59	*P*<0·001
Total number	300	162	462	
Per cent stenosed	15%	8·6%	12·7%	
>25 mm (long)				
Number stenosed	38	41	79	
Total number	166	160	326	
Per cent stenosed	22·9%	25·8%	24·2%	
Total				
Number stenosed	83	55	138	
Total number	466	322	788	
Per cent stenosed	17·8%	17·0%	17·5%	
	P>0·5			

Table 6. Effect of age and parity on cone biopsy length

	n	Percentage having long cones	Percentage stenosis in short cones	Percentage stenosis in long cones
Under 35 years	401	32%	12%	24%
Over 35 years	387	51%	13·7%	24%
Nulliparous	151	24%	11 3%	27%
Parous	637	46%	12·9%	24%

colposcopic assessment before cone biopsy and cone biopsy dimensions were available for 557 of them. The other 231 patients did not have a prior colposcopic assessment and cone biopsy dimensions were available in all of them.

Effect on cone biopsy length. Of the 557 patients who had a prior colposcopic assessment 257 had long cone biopsies removed; of the 231 patients who did not have prior colposcopic assessment 69 had long cones. This difference is significant ($P < 0{\cdot}001$). The proportions of 'short' and 'long' cones in colposcoped and uncolposcoped patients for each year of the study are presented in Fig. 3. This shows a trend towards the more frequent use of colposcopy and a trend toward longer cone specimens being taken over the 7 years of the study.

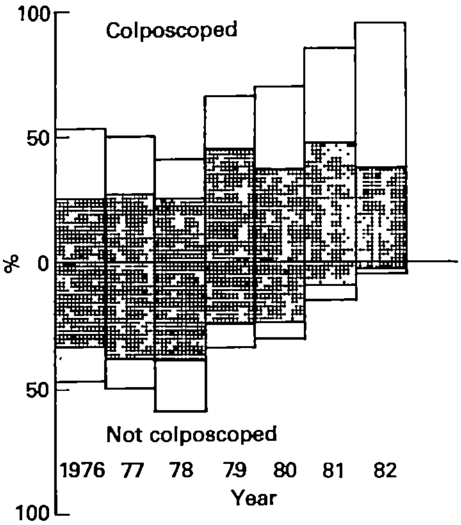

Fig. 3. The proportions of long (>25 mm, □) and short (≤25 mm, ▦) cones in colposcoped and uncolposcoped patients for each year of the study.

Effect on haemorrhage. The frequency of primary and secondary haemorrhage and measures taken to manage these complications in the colposcoped and 'uncolposcoped' group are presented in Table 7 and analysed according to the length of the cone specimen. Considering the two groups separately, there was a significant association between long cones and primary haemorrhage in the uncolposcoped group ($0{\cdot}02 > P > 0{\cdot}01$) but there were no significant differences in the prevalence of secondary haemorrhage or in any of the measures taken to manage haemorrhage. In the colposcoped group there were no differences between the patients who had long cones and those who had short cones in any of the haemorrhage characteristics. Primary haemorrhage occurred in 40 of the colposcoped patients and in six of the uncolposcoped patients. This difference is just significant ($0{\cdot}02 > P > 0{\cdot}01$) and is explained by the differing prevalences of haemorrhage in patients having short cones. None of the other haemorrhage characteristics differed significantly in the two groups.

Effect on cervical stenosis. The numbers of patients with cervical stenosis after short or long cone biopsies in both the colposcoped and uncolposcoped groups are presented in Table 7. Cervical stenosis was seen in 121 of 557 colposcoped patients (22%) and in 17 of 231 uncolposcoped patients (7%). Stenosis was observed more frequently after both long and short cone biopsies in colposcoped patients. When cone biopsy length is considered for each group separately, in the colposcoped group stenosis was observed in 52 of 300 patients who had short cones (17%) and in 69 of 257 patients who had long cones (27%) this difference was significant ($P < 0{\cdot}01$). In the uncolposcoped group stenosis was observed in seven of 162 patients with short cones (4%) and in 10 of 69 patients with long cones (14%). This difference also was significant ($0{\cdot}02 > P > 0{\cdot}01$).

In 305 of the colposcoped patients the squamocolumnar junction was not visualized; 159 (52%) of these patients had long cones removed. In 252 patients the squamocolumnar junction was visualized (but considered inaccessible in 118); 96 of these patients (38%) had long cones removed. This difference was significant ($P < 0{\cdot}01$).

Table 7. Effect of prior colposcopic assessment on haemorrhage and cervical stenosis

	n	Primary haemorrhage	Secondary haemorrhage	Hysterectomy	Blood transfusion	Resuture repack	Number stenosed *n* (%)	
Colposcoped								
Cone <25 mm	300	21	20	2	7	30	52 (17·3)	$P<0{\cdot}01$
Cone >25 mm	257	19	20	4	14	20	69 (26·8)	
Total	557	40	40	6	21	50	121 (21·7)	
Not colposcoped								
Cone <25 mm	162	1*	9	3	4	8	7 (4·3)	$P<0{\cdot}02$
Cone >25 mm	69	5*	6	–	4	8	10 (14·4)	
Total	231	6	15	3	8	16	17 (7·3)	

*$0{\cdot}027>P>0{\cdot}01$.

Discussion

The use of colposcopy with local destructive techniques for suitable lesions has reduced the proportion of patients in whom a cone is removed; in the period reviewed only 42% of patients with CIN were treated by conization (J. Jordan, personal communication). The most common indication for removing a cone after colposcopic assessment has become the failure to visualize the upper end of the transformation zone because the squamocolumnar junction lies too high in the canal; prior knowledge of upward extension is likely to influence the surgeon to cut a longer cone, in an attempt to ensure complete excision, and our results support this view.

Other workers have reported a relation between the length of cone and the occurrence of complications after its removal; for example, Claman & Lee (1974) found an increased frequency of haemorrhage in longer cone biopsies, and its seems reasonable to accept that haemorrhage, especially secondary haemorrhage, is related to the area of the bed left after removal. In our study the overall relationship between cone length and haemorrhage was not statistically significant, but our figures do indicate an association between cone length and stenosis; such an association has not been recorded before but the incidence of stenosis we met with is higher than that in most reports.

The rates of stenosis reported after cone biopsy vary greatly and it is unfortunate that there is no accepted objective standard for measuring stenosis. Schulman & Ferguson (1962), who defined stenosis as the inability to pass a standard uterine sound, found a rate of 3%, Hollyock & Chanon (1972) 3%, and McCann *et al.* (1969) 0.6%. In sharp contrast Byrne (1966) found stenosis in 31% and two-thirds of his patients required dilatation of the canal. That stenosis is a problem was recognised by Villasanta & Durken (1969). Crisp *et al.* (1968) and Rubio *et al.* (1975) performed routine cervical dilatation within 6 weeks of conization and did not mention later stenosis. Our relatively high rate of 17% reflects the follow-up procedure used; most of these observers quoted relied on simple inspection or probing but awareness of stenosis is increased by the use of the colposcope, both allowing and demanding accurate identification of the new squamocolumnar junction which may lie within the narrowed canal. Cervical stenosis was symptomatic in only 8% of our patients but it is important in all patients because it affects the practical management of patients after conization, since anatomical distortion can prevent both colposcopic and cytological examination.

That post-conization stenosis is increased by more accurate, preoperative assessment seems paradoxical, but the use of local destructive techniques leads to the exclusion from operative treatment of lesions that might have once produced smaller cones and thus fewer complications. Nevertheless, a reduction in the occurrence of complications and in particular stenosis might result from a further refinement in preoperative diagnosis; we feel the development of more precise techniques, such as hysteroscopy, for the length of the canal involved by a lesion, to be desirable, provided that they do not jeopardize histological assessment, which is in itself an important part of management. If the length of cervix to be excised could be measured accurately the size of the cone could be left to a minimum, reducing complications due to the removal of over long specimens. The possibility of reducing scarring by other less traumatic techniques of conization, such as laser excision, should also be considered.

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Spontaneous resolution of cervical warty atypia: the relevance of clinical and nuclear DNA features: a prospective study

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Summary. A selected group of 51 patients with histological features of cervical warty atypia was observed for 1 year. Initial features were compared with a cohort of 50 patients with CIN. Twenty-four patients showed resolution of the warty atypia, in 19 it remained unchanged, and in eight patients CIN or microinvasive disease was present on repeat biopsy. The DNA patterns obtained by tissue imprint of the initial biopsies and subsequent integrated densitometry, using a Vickers M85 scanning densitometer, showed that warty atypias could be objectively distinguished from CIN, but that the method could not predict the group of warty atypias that would resolve. There was no clinical feature or group of features which allowed a means of predicting the outcome of such lesions.

Cervical intraepithelial neoplasia (CIN) has well-documented cytological, histological and colposcopic criteria for diagnosis. Similarly, distinctive criteria are available for warty atypia or non-condylomatous wart virus infection (Meisels & Fortin 1976; Meisels *et al.* 1977; Zur Hausen 1977; Reid *et al.* 1980; Meisels *et al.* 1981), due to the presence on the cervix of papilloma virus. Papilloma virus infections have a well-documented potential for malignant transformation, both in animals (Kreider 1980) and in man (Jablonska *et al.* 1972; Atkin 1976). An aetiological relation between warty atypia and CIN has been proposed (Zur Hausen 1977).

Having established our criteria for diagnosis of cervical warty atypia (Kirkup *et al.* 1982) we report here the results of following 51 patients with untreated cervical warty atypia for a period of 1 year.

Patients and methods

From May 1981, we assessed all the patients referred to the colposcopy clinic with an abnormal smear. Each patient was assessed at the first clinic visit in a standard manner: a full clinical history was followed by colposcopic examination of the cervix, squamocolumnar junction, and vaginal fornices, together with a repeat cervical smear, colpophotograph and directed punch biopsies of the colposcopically abnormal areas. The presence or absence of the colposcopic features shown in Table 1 and the exact biopsy sites were noted at the time of colposcopy. Histological and cytological material from each patient was independently reviewed, and biopsy material used to form a tissue imprint for subsequent densitometry assessment as described elsewhere (Nasiell *et al.* 1979; Evans & Monaghan 1983).

All patients were reviewed 1 month after the first visit and were allocated to the study or treatment groups as shown in Table 2. The criteria for the histological diagnosis of warty atypia has been described previously (Kirkup et al. 1982).

All patients in the treatment group had CIN treated with the CO_2 laser. The study group were reviewed at colposcopy every 3 months. At each

Table 1. Colposcopic, histological and cytological features of patients in the study

Colposcopic	Histological	Cytological
Aceto-white epithelium	Koilocytosis	Koilocytosis
Mosaic pattern—open	Double nucleation	Double nucleation
Mosaic pattern—regular	Dyskeratosis	Dyskeratosis
Area of cervix involved—quadrant number	Subdermal round cell infiltrate	
Variable contour	Abnormal mitotic figures	

Table 2. Criteria for patients considered in this study

Treatment group (n = 50) Histology reported as CIN only	Study group (n = 51) Histology suggested a warty atypia

Exclusions
1 > 35 years of age
2. Smear grade V
3 Abnormal vessels on colposcopy
4. Endocervical lesion
5. No abnormality on biopsy
6. Pregnancy

visit the cervical lesion was observed, drawn, photographed and a cervical smear was taken. Patients were removed at any time, if the criteria were not fulfilled at each visit. Poor attenders were also excluded from the study (a total loss of three patients leaving 51 to complete the year).

Feulgen densitometry

Imprints were taken of biopsied samples at initial colposcopy. These were taken by impressing the biopsy onto a plain glass slide and methodically moving the biopsy over the slide. The cellular material was air dried for 60 s and then placed in 50–50 ether alcohol fixative. The remaining biopsy material was fixed in Susa for subsequent histological examination. The exact method of Feulgen staining has been described more fully elsewhere (Evans & Monaghan 1983). Integrated scans were carried out using a Vickers M85 Scanning Densitometer at 545 nm with background subtraction. From each imprint preparation, 100 epithelial nuclei were assessed. Thirty small lymphocyte nuclei in each slide were measured as controls. Using the mean DNA value for these lymphocyte nuclei as a $2n$ control the frequency distribution of the epithelial cells in the preparation was then plotted on a logarithmic scale to illustrate tumour cell nuclei having a ploidy state near to that of the normal lymphocytes ($2n$) and those of higher modal values.

Assessment at 1 year

Thirteen months from the first visit, all patients were examined colposcopically together with a repeat cervical smear, colpophotographed, and biopsies were taken from any colposcopically abnormal area or an area approximating to the first biopsy site where there was no colposcopic abnormality. Any lesion still present was subsequently treated using the CO_2 laser. Resolution was judged to have occurred where there was no evidence of residual disease using cytology, colposcopy and histology.

Results

Initial assessment

There were 50 patients in the treatment group and 51 patients in the prospective study group. These two groups were compared for age, age at first coitus, age from first coitus to attendance at the clinic and the grade of smear at first visit to the colposcopy clinic. There was no statistical difference (using the Kolmogrov–Smirnov test) between the two groups. But there was a statistical difference in lesion size; the warty atypia group had much the larger lesions.

Densitometry

Both groups had tissue imprints taken at the first visit, for Feulgen-stained densitometry analysis. Examples of the histograms obtained are shown in Figs 1 and 2 where the nuclear density is expressed in arbitrary units (a.u.). As can be seen from Table 3, CIN lesions showed a predominantly aneuploid pattern, and warty atypias a polyploid pattern, but in 13 cases no

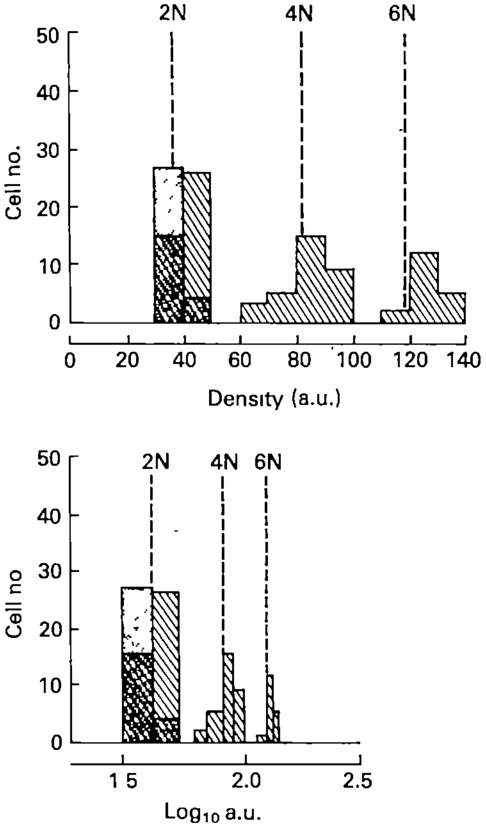

Fig. 1. DNA histogram from warty atypia. ▨ Epithelial cells; ☐ small lymphocytes.

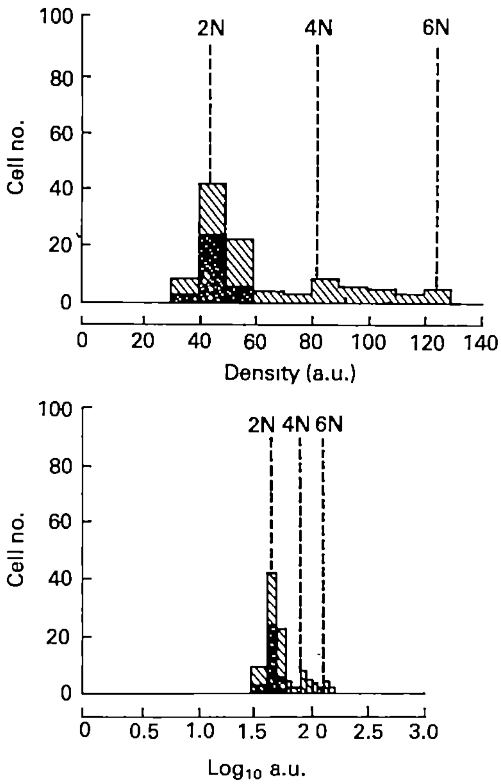

Fig. 2. DNA histogram from CIN lesion. ▨ Epithelial cells; ☐ small lymphocytes.

imprint was obtainable, and in 18 a normal densitometric pattern was established.

Table 4 shows the incidence of the features documented at first assessment and at 1 year. Of the 51 patients, 24 had a resolution of the cervical warty atypia. No single clinical feature or group of features could be identified as a significant pointer to resolution.

Resolution of the warty atypia occurred in 18 of the 34 patients with a polyploid DNA pattern on densitometry but in none of the five patients with an aneuploid cell line.

At 1-year assessment and biopsy, six patients had developed CIN. One patient had CIN 3 with gland infilling, one patient had microinvasive disease removed by conization.

Discussion

Spontaneous resolution of abnormal cervical cytology is frequently observed (Kottmeier 1953; Peterson 1956; Koss *et al.* 1963). In this prospective study, we have differentiated CIN from cervical warty atypia and have shown that resolution occurred in 50% of warty atypias over 1 year.

In our earlier work we found that patients with cervical warty atypia tended to be in their early

Table 3. Histopathology and ploidy patterns of the tissue imprints

	Ploidy pattern				
Histopathology	None	Euploidy	Polyploidy	Aneuploidy	Total
CIN	9	10	1	30	50
Warty atypia	4	8	34	5	51

reproductive years and there was an increase in endocervical CIN lesions after the age of 35 years. This study does not show any sharp division in the age groupings for CIN and warty atypia when compared for age, or age from first intercourse to clinic attendance, because all patients selected were under 35 years. Our results *do* show that the lesion of warty atypia is more extensive than that of CIN, confirming previous findings (Evans *et al.* 1984).

Nuclear DNA densitometry was undertaken as an ancillary investigation, and showed that CIN lesions and cervical warty atypia could be objectively differentiated, the CIN lesions showing a mainly aneuploid pattern, whereas most warty atypias showed a polyploid DNA pattern, with a modal count of up to 8*n*; these polyploid DNA values may be an expression of intranuclear papilloma virus with abnormal genome function, or may reflect a function of cell division inhibition. As can be seen in Table 4, densitometry could not predict the lesions which would resolve, only the groups within which some patients would show resolution of their lesions It is of interest that, even with strict criteria of diagnosis for cervical warty atypia, some of these lesions contained an aneuploid cell line, none of which resolved spontaneously. Imprint densitometry is a useful research technique to differentiate objectively warty atypia from CIN, but cannot be used for clinical differentiation, since there are too many falsely normal results.

Table 4. Features at first assessment of the study group

	Initial incidence (*n* = 51) *n*	%	Features of resolved group (*n* = 24) *n*	%
Cytology				
Koilocytes	5	(10)	3	(12·5)
Double nuclei	27	(53)	8	(33·3)
Dyskeratosis	11	(22)	3	(12·5)
Nuclear enlargement	16	(32)	13	(54·2)
Colposcopy				
Mosaic—open	42	(84)	17	(70.8)
Mosaic—regular	4	(8)	3	(12·5)
Satellite lesions	22	(44)	12	(50)
Quadrant No. 1	11	(22)	5	(20·8)
2	11	(22)	5	(20.8)
≥3	29	(58)	14	(58)
Variable contour	31	(62)	13	(54·2)
Histology				
Koilocytosis	49	(98)	24	(100)
Double nucleation	48	(96)	24	(100)
Dyskeratosis	46	(92)	20	(83)
Round cell infiltrate	18	(36)	9	(37·5)
Abnormal mitoses	30	(60)	11	(45·8)
Densitometry				
None	4	(8)	3	(12·5)
Aneuploid	5	(10)	0	(0)
Euploid	8	(16)	3	(12·5)
Polyploid	34	(67)	18	(75)

Our results show that within a period of 1 year, half of the warty atypia lesions resolved, 19 patients remained unchanged, and in eight patients the review biopsy showed a CIN lesion or microinvasion. Analysis of our observations showed no one feature or group of features which sign-posted resolution. On the basis of these results, it appears that warty atypias on the cervix behave in the manner of a low-grade, slowly resolving infection, and resemble the progression of the similar Shope rabbit papilloma virus, with 50% of the lesions remaining unchanged (Kreider 1980). Cytology, whilst of use as a screening technique to alert the clinician, does not differentiate between CIN and warty atypia, and does not show any features which aid in suggesting resolution. Patients with grade IV smears should be colposcopically assessed even where there is cytological evidence of double nucleation, koilocytosis and dyskeratosis inferring viral infection, since there may be a concomitant CIN lesion present.

In the unresolved group lesions occurred which progressed to CIN and mircroinvasive disease; this emphasizes that all warty atypias should be treated, as the potential for malignant transformation is still undetermined, and the possibility of undiagnosed coincident CIN with progression is ever present.

Acknowledgments

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Malakoplakia of the pelvic peritoneum in pregnancy. Case report

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Case report

The patient was a 30-year old Mauritian woman, resident in England for 10 years. In 1978 she had an emergency caesarean section, in labour, for fetal distress. No intra-abdominal abnormality was noted. In 1981 an attack of lower abdominal pain led to a laparotomy and appendicectomy. The fallopian tubes appeared mildly inflamed, but were not biopsied. The appendix showed mild serosal inflammation but no evidence of malakoplakia. In 1982 she aborted at 11 weeks gestation; the curettings did not show malakoplakia.

In 1983 she became pregnant for the third time. At 20 weeks gestation she was admitted complaining of a sudden attack of suprapubic and bilateral loin pain, together with frequency, dysuria, diarrhoea and vomiting. She was apyrexial and distressed, with tenderness and guarding in the lower abdomen and tenderness in the right renal angle. A mid-stream urine culture (MSU) revealed a significant ($>10^5$ bacteria/ml) growth of coliform bacteria; the infection responded clinically to ampicillin. During the 33rd week of pregnancy she was re-admitted with generalized abdominal pain mainly localized in the epigastrium and right iliac fossa. There were no associated urinary symptoms. A further MSU was sterile. A cystoscopy was not performed. The pain settled without further treatment.

The pregnancy then proceeded uneventfully until 39 weeks when an elective caesarean section was performed in view of her previous section and a narrow funnel-shaped pelvis shown on X-ray pelvimetry. All of the pelvic organs were found to be covered in a brown film which contained many small brown tomato seed-like nodules. The filmy plaques peeled easily off the visceral peritoneum. A biopsy showed typical features of malakoplakia, with sheets of large histiocytes predominating. The cytoplasm of the histiocytes was granular. Sections stained with methanamine silver and PAS methods showed a mixture of small and large granules. The larger granules showed the microspherular appearance of Michaelis–Gutmann bodies (Fig. 1). The patient made an uneventful recovery.

Discussion

Malakoplakia is an unusual form of histiocytic inflammatory reaction found in association with coliform infections. It was originally described at the turn of the century (Michaelis & Gutmann 1902; von Hansemann 1903). The term refers to the soft yellowish-brown plaques which characterize the condition. They are found in numerous sites including the urinary bladder, the gall bladder, the colon, the endometrium and the testis (Thomas *et al.* 1978). The plaques consist of large numbers of histiocytes which have PAS-positive cytoplasm, often containing Michaelis–Gutmann bodies. Electron microscopy shows that bacteria are present within the cytoplasm of these cells and also within the Michaelis–Gutmann bodies (McClurg *et al.* 1973, Willén *et al.* 1983).

It seems to be unlikely that these patients are infected by an unusual strain of coliform or have a defect of cell-mediated immunity. An abnormality of intra-cellular digestion of the phagocytosed bacteria is the most likely explanation (Lou & Tepitz 1974; Thorning & Vracko 1975; Lewin *et al.* 1976). The bacteria are found within the cells, in large phagolysosomes, which even-

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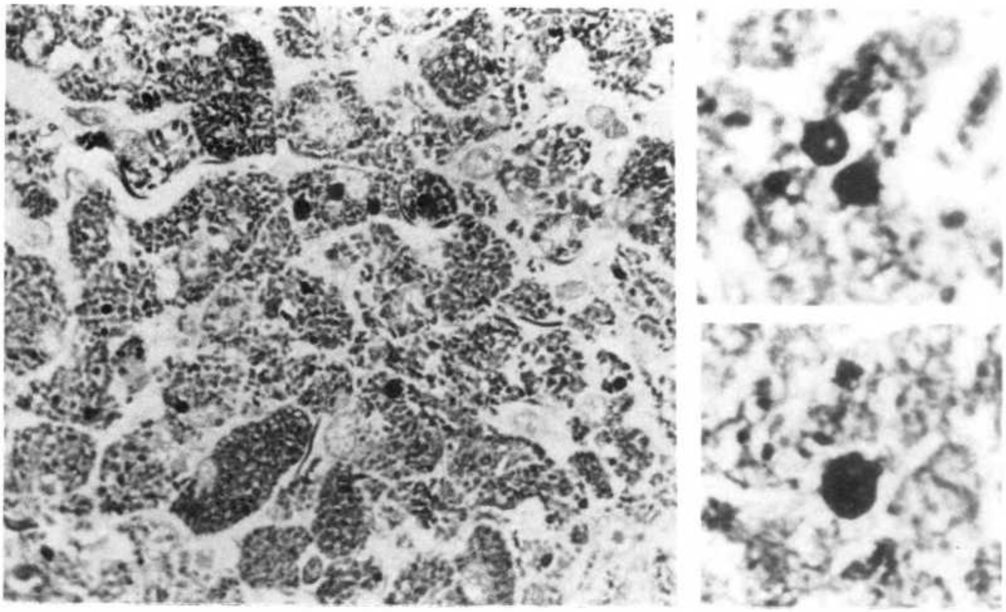

Fig. 1. Sheets of histiocytes contain granular material in their cytoplasm. Methanamine silver magnification × 128. Insets: similar Michaelis–Gutmann bodies. Methanamine silver magnification × 320.

tually become mineralized, forming concentric spherules which we recognize as Michaelis–Gutmann bodies. These stain positively for iron and calcium.

Although very occasional fatal cases have been reported the condition seems to be self limiting, especially after appropriate antibiotic treatment (Yunis *et al.* 1967). One case of recurrent endometrial malakoplakia has been reported in an elderly diabetic patient (Molnar & Poliak 1983).

The present patient appears to be the first reported in which the serosal surface of the pelvic organs has been involved. The patient suffered from a coliform urinary tract infection during pregnancy. The character of the patient's symptoms was consistent with a urinary tract infection, but it is possible that the reaction present in the pelvic peritoneum was responsible for her attacks of lower abdominal pain. Nevertheless in the presence of proven infection, no further treatment appears to be indicated over and above appropriate antibiotic therapy.

Acknowledgment

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Excessive testosterone secretion in pregnancy. Case report

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Case report

An 18-year-old girl presented with 3 months' amenorrhoea following previously regular menses. She was markedly hirsute, but denied that this was either a problem or increasing in amount. She was taking no medication. On examination she had a normal female habitus with excessive facial, abdominal, limb and perineal hair in a male distribution. The clitoris was possibly enlarged, the uterus was slightly enlarged and there was a small mass in the left appendage. Pregnancy was confirmed associated with high testosterone levels (see Table 1). At 18 weeks, she developed left iliac fossa pain and vomiting with signs of peritonism and the suggestion of an enlarged left ovary on ultrasound scanning. At laparotomy, both ovaries were slightly enlarged with no evidence of torsion. Cruciate transection revealed no evidence of a tumour. The left-sided corpus luteum and representative sections were excised for histological and biochemical analysis. Blood was also drawn from the ovarian vessels. The pregnancy continued to term, complicated by mild hypertension. A live male infant was born spontaneously with no evidence of precocious development. The placenta was normal. The patient remained hirsute but after 5 months commenced combined oral contraception and began to shave her legs.

Materials and methods

Venous blood was obtained and the plasma separated within 4 h and stored at −20°c.

Plasma testosterone was analysed in two assays—the routine hospital assay using a Nordiclab kit (assay 1) and in a specialized androgen laboratory (assay 2) which also allowed for the measurement of androstenedione, dehydroepiandrosterone (DHEA) and its sulphate (DHEAS), all following ether extraction and celite column fractionation according to the methods of Anderson *et al.* (1976). The latter assays were performed in two batches.

Sex hormone-binding globulin (SHBG) was assayed using the two-tier column technique of Iqbal & Johnson (1977).

Urinary steroids were determined by gas–liquid chromatography with capillary columns analysing methyloxime-trimethylsilyl ether derivatives with a gas chromatograph attached to a mass spectrometer (Shackleton & Honour 1976).

Biochemical analysis of the ovary was performed after crude dissection of 5–10 mg portions of tissue. This was homogenized as far as possible in a Braun homogenizer in buffer solution and then extracted with ether. The extract was redissolved in iso-octane and the steroids assayed after fractionation in celite–propylene glycol columns.

Results

Plasma testosterone levels were elevated throughout pregnancy rising to a peak (52 nmol/l) at delivery, a level well above the normal range for men. By comparison, 12 normal women in the third trimester had a mean plasma testosterone of 4·7 (SD 1·5) nmol/l (assay 1). Plasma androstenedione and testosterone levels rose in parallel. DHEA and DHEAS levels by contrast were low, consistent with pregnancy and with an ovarian rather than adrenal source for the androgen production. SHBG levels were elevated consistent with pregnancy but were lower than in a small group of normal controls. At delivery cord blood showed androgen levels consistent with a male child. By 6 weeks post-

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Table 1. Plasma steroid and sex hormone-binding globulin (SHBG) concentrations

Time of sampling	T (nmol/l)		A (nmol/l)	DHEA (nmol/l)	DHEAS (µmol/l)	SHBG (nmol DHT bound/l)
	Assay 1	Assay 2				
Gestation (weeks)						
11	9·6	—	—	—	—	103
15	13·0	15·8	25·6	11·3	—	—
17	22·0	22·1	23·8	12·4	—	—
20 (at laparotomy)						
Peripheral vein	—	14·3	29·0	9·6	—	—
Left ovarian vessels	—	148·3	1028·0	145·0	—	—
Right ovarian vessels	—	35·3	269·0	60·0	—	—
20 (5 days after laparotomy)	13·6	7·0	23·2	8·8	—	—
34	34·4	30·4	56·0	—	1·8	222
41 (At delivery)	30·7	52·2	56·0	—	1·4	229
Cord blood	—	3·7	12·0	—	4·6	21
Postpartum						
6 weeks	3·6	3·0	14·4	—	2·0	60
4 months	6·3	—	—	—	—	—
6 months (taking oral contraceptives)	1·6	—	—	—	—	—
Non-pregnant women (normal range)	0·5–2·5	0·4–2·0	2·0–8·5	10–40	2·2–2·9	50–100

T, Testosterone; A, androstenedione; DHEA, dehydroepiandrosterone; DHEAS dehydroepiandrosterone-sulphate; DHT dihydrotestosterone.

Table 2. Urinary steroid excretion at 16 weeks gestation compared with three normal pregnancies at 16 weeks

	Patient FG	Controls		
		N1	N2	N3
Androsterone	3080	550	1530	610
Aetiocholanolone	440	460	820	200
11β-hydroxyandrosterone	540	300	940	360
11β-hydroxyaetiocholanolone	90	270	400	440
Pregnanediol	380	1890	4040	1560
Pregnane-3α-17α,20α-triol	620	310	880	220
Androstene-3β, 16α, 17β-triol	740	190	540	120
Oestriol	150	780	1340	270
16α-hydroxypregnenolone	280	220	470	180
Tetrahydrocortisone	740	520	1380	270
Tetrahydrocortisol	300	220	380	110
5α-tetrahydrocortisol	760	70	530	20
α-cortolone	360	90	290	140
β-cortolone	30	90	250	100

Results are given as µg/day.

partum, maternal androgens had fallen to levels consistent with a mild degree of androgen excess such as is found in women with idiopathic hirustism. After treatment with a combined 50 µg ethinyloestradiol-progestogen pill (Ovulen 50), testosterone levels became normal (Table 1).

Urinary steroid analysis showed high levels of androsterone, presumably a metabolite of testosterone or androstenedione (Table 2).

The ovarian vein samples showed very high levels of androgen from the left side, while the tissue analysis showed high levels of androgen

Table 3. Ovarian tissue biochemistry

Description	Androstenedione		DHEA		Testosterone	
	R	L	R	L	R	L
Tough white outer coat of ovary	1·55	0·58	1·62	0·87	0·95	0·27
Red 'pulpy' central tissue	0·37	0·37	0·66	0·56	0·61	0·47
Wedge of white and red	0·37	—	—	—	0·39	—
Corpus luteum	—	0·67	—	0·26	—	0·65

All results expressed as µg steroid/mg wet tissue (after defreezing).
R, Right ovary; L, left ovary.

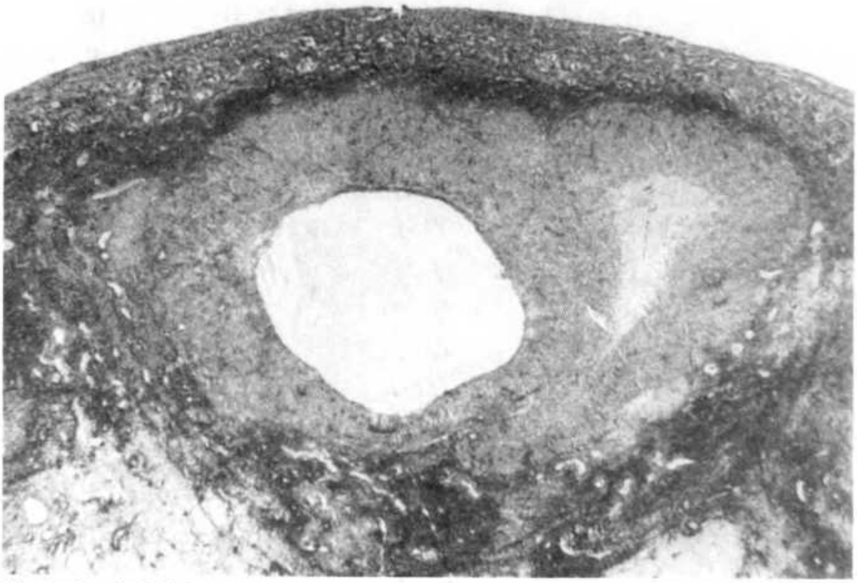

Fig. 1. Atretic follicle surrounded by hyperplastic luteinised theca cells. ×25.

particularly from the right ovarian capsule and to a lesser extent from the (left-sided) corpus luteum (Table 3).

Histology of the two ovaries showed similar appearances. All the developing and atretic follicles were surrounded by broad bands of hyperplastic luteinized theca cells (Fig. 1). The corpus luteum weighed 10 mg and appeared normal, surrounded by a narrow band of normal theca cells.

Discussion

A modest increase in circulating androgens is well documented in pregnancy (Gandy 1977; Gibson & Tulchinsky 1980), although the relative contribution from ovaries or adrenals has not been established. The increase in testosterone accompanies an oestrogen-mediated rise in the levels of SHBG, which modulates the availability of free testosterone (Forest *et al.* 1971).

Excess androgen production is rare in pregnancy. While many of the reported cases have discussed urinary androgens, very high levels of plasma testosterone have only been recorded in 18 patients in the English literature, and all of them had ovarian pathology to account for the androgen production (Table 4). All were investigated for the onset of virilization in pregnancy, although three had previously been hirsute. Levels of plasma testosterone varied from 8 to 520 nmol/l. Only three of the eight female fetuses showed any evidence of *in utero*

Table 4. Case reports with excessive plasma testosterone levels in pregnancy

Author	Max. recorded testosterone level (nmol/l)	Time of sample*	Histology	Mother	Fetus
Berger *et al.* (1984)	74	At delivery	Polycystic ovaries	Virilized in pregnancy	Normal female
Connor *et al.* (1968)	6·6	9 days after delivery	Krukenberg tumour	Virilized in pregnancy	Female with clitoromegaly
Fayez *et al.* (1974) 1	34	1 day before delivery	Polycystic ovaries	Previously hirsute & obese	Normal female
2	34	2 days after delivery	Polycystic ovaries	Previously hirsute & obese	Normal male
Forest *et al.* (1978)	156	7 days after delivery	Krukenberg tumour	Virilized in pregnancy	Female with clitoromegaly
Forti *et al.* (1976)	269	15 weeks gestation	Luteoma	Hirsute & acne in pregnancy	Normal male aborted after surgery
Gilliland & McCollough (1972)	122	31 weeks (proceeded to term)	Hilus cell tumour	Virilized in pregnancy	Normal male
Hensleigh *et al.* (1975)	520	At delivery	Hyperreactio	Previously hirsute	Normal female
Hensleigh & Woodruff (1978)	49	At delivery	Hyperreactio	Virilized in pregnancy	Normal twins, male/female
Jewelewicz *et al.* (1971)	51	Day after delivery	Polycystic ovaries ?luteoma	Virilized in pregnancy	Normal female
Judd *et al.* (1973)	485	8 weeks after delivery	Bilateral theca lutein cysts	Virilized in pregnancy	Normal twins, male/female
Magendantz *et al.* (1972) Case 3	60	8 weeks gestation	Luteinized theca	Recurrent virilization in pregnancy	Aborted
Novak *et al.* (1970)	184	Day before delivery	Mucinous cystadenoma with stromal hyperplasia	Virilized in pregnancy	Normal male
Polansky *et al.* (1974)	106	At delivery	Bilateral luteoma	Virilized in pregnancy	Normal male
Thomas *et al.* (1972)	21	2 days after delivery	Bilateral luteoma	Virilized in pregnancy	Normal male
Verhoeven *et al.* (1975)	8	At delivery at 36 weeks	Mucinous cystadenoma with theca lutein stromal change	Virilized in pregnancy	Normal male
Wolff *et al.* (1973)	16	7 days after delivery	Luteoma	Virilized in pregnancy	Female with clitoromegaly
Zander *et al.* (1978)	208	At 32 weeks (before surgery)	Luteoma	Virilized in pregnancy	Normal male

* 'Delivery' was at term, unless otherwise stated.

masculinization. None of them had testosterone levels measured at delivery in either mother or fetus, while the levels noted at about a week postpartum were all lower than those recorded in other patients with normal female fetuses. None of these studies reported any SHBG levels.

Our patient is unusual in that she presented with amenorrhoea rather than hirsutism as her main symptom, and with the finding of a pregnancy, the moderately elevated testosterone level was almost ignored. However, the rising levels and the onset of left-sided symptoms prompted a laparotomy to exclude a tumour undergoing torsion. Amniocentesis for karyotyping was contemplated at the time of surgery but was eventually avoided as the risks of fetal virilization were thought to be less than that of subsequent abortion.

The steroid levels in both the blood and urine obtained at laparotomy seem rather confusing and contradictory in the light of the similar histology from each ovary. It was difficult, however, to be sure that the blood obtained was pure venous effluent and this may have affected the results. Despite this the high levels of steroid obtained would support the hypothesis that the hyperplastic theca cells were the main source of the circulating androgens.

The histological picture suggested the possibility of theca cell hyperplasia mediated by hCG as in a molar pregnancy. There was no evidence of molar degeneration in the placenta. However, the rise in androgen production continued through the pregnancy up to delivery, and then subsided by 6 weeks postpartum to levels consistent with polycystic ovarian syndrome. Unfortunately hCG and gonadotrophin levels are not available in this patient except at her first visit. It would have been of interest to have measured these in cord blood along with oestrogen levels to assess both the degree of stimulation of the ovaries and the capacity of the placenta to aromatize the excess androgen, as discussed by Hensleigh & Woodruff (1978).

It may well be that polycystic ovaries do synthesize excessive androgen in pregnancy but very little data is available at the present time. Further studies are in progress to document this.

Acknowledgments

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SHORT COMMUNICATIONS

Lactation in placental steroid sulphatase deficiency

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Placental steroid sulphatase deficiency (PSD) is an inborn error of metabolism inherited as a recessive X-linked trait (Shapiro 1983). The incidence appears to be approximately 1 per 2000 male births (Lykkesfeldt *et al.* 1984). Postnatally, all affected boys acquire ichthyosis of the recessive X-linked type (RXLI), a chronic disorder of keratinization usually with large brownish scales covering most of the body surface, but sparing the face, palms and soles. The underlying abnormality of RXLI has been shown to be a deficiency of steroid sulphatase activity in the skin, leucocytes, and in other tissues as well (Shapiro 1983).

The normal placenta has a high steroid sulphatase activity and the enzyme is essential for the hydrolysis of sulphated androgen precursors, such as dehydroepiandrosterone sulphate, from the fetal adrenals before they can be aromatized to oestrogens in the placenta. Consequently, PSD results in extremely low levels of both fetal and maternal oestrogens. Until now, approximately 100 patients with PSD have been described (Lykkesfeldt *et al.* 1984), but little attention has been given to the clinical significance of this enzyme disorder for postpartum lactation. Martin & Oakey (1982) reported 10 women with PSD who attempted to establish breast-feeding; none was breast-feeding 10 days postpartum and the authors concluded that adequate oestrogen stimulation during pregnancy was required for successful lactogenesis. This finding has prompted us to review 25 of our patients with PSD, and interview the women specifically about lactation. All of them fulfilled the criteria of PSD: extremely low oestriol levels during pregnancy; in-vitro verification of steroid sulphatase deficiency postpartum; and RXLI in the boys as reported previously (Lykkesfeldt *et al.* 1984). Of the 25 women, 23 had desired to breast-feed and 20 of them were lactating 10 days postpartum, as detailed in Table 1. Thus only three of these women failed to establish lactation and an adequate explanation was found in each: premature twins, insufficient nursing instruction; and separation of child and mother in the first few days postpartum, respectively. Three women who established lactation stopped breast-feeding after $\leqslant$1 month due to maternal complications after caesarean section for twins, insufficient weight-gain of the infant, or neonatal hyperbilirubinaemia.

Table 1. Duration of lactation in 23 women with placental steroid sulphatase deficiency who wanted to breast-feed

Duration of lactation	Number of women
No lactation	3
$\geqslant$10 days	20
$\geqslant$1 month	17
$\geqslant$2 months	15
$\geqslant$6 months	9

We conclude that women whose pregnancies have been complicated with PSD can be safely encouraged to breast-feed as they are generally as successful in this as other women. Moreover, it can be inferred that low antenatal levels of oestrogens have little if any influence on lactogenesis.

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A simplified approach to oocyte recovery for in-vitro fertilization

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The availability of in-vitro fertilization within the Health Service has been limited by the resources needed to monitor ovulation and perform laparoscopy under general anaesthesia. We describe our experience with a simplified approach that uses ultrasound to monitor follicular development in women with clomiphene-controlled cycles followed by out-patient oocyte recovery using a modification of the percutaneous transvesical ultrasound guided approach, first described by Lenz *et al.* (1981).

Patients, methods and results

Nineteen patients were studied in 37 cycles. They were all slim volunteers and had been infertile for between 3 and 11 years. The infertility was considered to be unexplained in seven couples and in the remaining 12 couples it was related to the absence of cervical mucus (5), oligozoospermia (4), endometriosis (2), and tubal blockage (1).

Ovulation was stimulated with clomiphene, 100 mg daily, from the first to the fifth day of the menstrual cycle, which led to the development of one large follicle in most women. Daily ultrasound measurement of the mean follicular diameter was begun on the ninth day of the cycle, using a small wheel mechanical sector scanner (ATL Mark III with a 3MHz probe). When one or more follicles had attained a diameter of at least 18 mm, 5000 i.u. of human chorionic gonadotrophin (hCG, Profasi, Serono) was given by intramuscular injection. The injections were usually given at 23.00 hours with oocyte recovery planned for 35 h later. This allowed clinical and laboratory work to be completed during normal working hours.

In 15 of the 37 cycles ultrasound examination before planned recovery suggested that ovulation had already occurred, and so recovery was not attempted. In the remaining 22, the skin over the bladder was infiltrated with 10 ml of 0.5% lignocaine. A 19 cm, 16 gauge spinal needle was passed into the bladder and clamped to the ultrasound transducer, ensuring that the aspirating needle lay in the plane of the ultrasound scan (Fig 1). This outer needle permitted the infusion of warm sterile saline into the bladder to give optimal bladder distension. Under ultrasound visualization a 29 cm, 19 gauge needle with a trocar-pointed stilette was passed through the outer needle, through the back wall of the bladder, and into the follicle. The trocar point on the stilette helped to steady the ovary during penetration of the follicle. The contents of the follicle were aspirated into a tissue culture tube, and the follicle then flushed with culture medium. Follicular aspiration was achieved in 18 of the 22 attempts. One woman ovulated from her most mature follicle during ultrasonic examination immediately before aspiration, and a second small follicle produced follicular fluid only. In two other women the aspirate confirmed a presumptive ultrasonic diagnosis of follicular cysts. Eleven oocytes were recovered from the remaining 15 patients in whom aspiration was successful (Table 1).

Most patients found the procedure uncomfortable, particularly the distension of the bladder. Supplementary analgesia was provided

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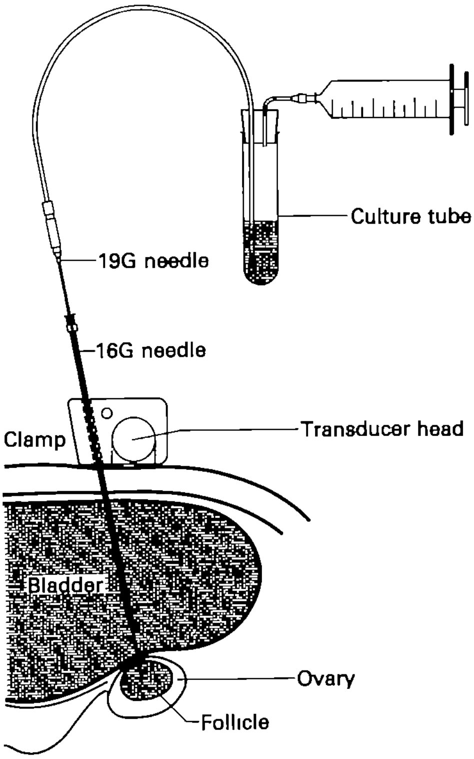

Fig. 1. Double needle technique for aspirating follicles

on request by means of Entonox or trilene inhalation. The only complication noted was transient haematuria in four women.

Six of the 11 oocytes recovered were fertilized and began to cleave. Embryo transfer was carried out using a Craft embryo transfer catheter: ultrasound visualization assisted the operator to negotiate the cervical canal, and measurement from the tip of the outer cannula to the uterine fundus allowed accurate placement of the catheter containing the embryo.

Discussion

The double needle technique described has several advantages over the method described by Lenz *et al.* (1981). The bladder can be rapidly filled or emptied without the need for urethral catheterization. The aspiration needle passes through a sterile channel uncontaminated by ultrasound couplant, and so cumbersome methods of shielding the unsterile ultrasound transducer are not required. The external needle reduces the flexion of the aspirating needle as it encounters the resistance of the ovarian tissue and also the reduced friction, compared to the direct passage of the aspirating needle through the tissues of the abdominal wall, allows more precise manipulation of the aspirating needle. The tips of both needles are readily visualized with ultrasound, which assists targetting of the follicle. Finally, the apparatus is cheap, with much of it being available from standard suppliers of medical equipment.

The oocyte recovery rate, although lower than that achieved using laparoscopic techniques, was similar to that reported by other workers using ultrasonic techniques (Lenz *et al.* 1981; Wikland *et al.* 1983). The use of larger needles may improve oocyte recovery rates, but has required the use of general anaesthesia (Wikland *et al.* 1983). The choice of an ovarian stimulation regimen that reliably develops multiple follicles and the use of additional measurements to predict ovulation should result in more follicles being available for aspiration in each cycle. Overall success rates might therefore be expected to improve with experience.

This simplified approach does not require rapid hormone assay systems to monitor follicular development or operating theatre facilities for laparoscopic oocyte recovery. The avoidance of general anaesthesia increases the number of cycles in which it is safe to offer treatment, giving individual couples a greater chance of pregnancy. Out-patient treatment allowed couples to participate throughout the procedure which may be of benefit in reducing the stress involved in in-vitro fertilization

Table 1. Attempted oocyte recovery in 37 cycles

Ovulated already	15
Dry tap	4
Follicular fluid only	8
Oocytes recovered*	10

*11 oocytes recovered from 10 women.

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BLAIR BELL RESEARCH SOCIETY

Papers presented at the meeting in Birmingham on 15 September 1984

The effect of low maternal weight on birthweight in a multiracial population by P. B. Terry & R. G. Condie. Department of Obstetrics and Gynaecology, Dudley Road Hospital, Birmingham

The crude birthweight and neonatal ponderal index (Rohrer) of 2934 normally formed singletons born to a population of mixed ethnic origin (European, West Indian, Pakistani and Indian) were analysed with reference to low maternal weight and low maternal weight-related indices. The indices used were the maternal weight at 20 weeks gestation, the maternal weight index (Quetelet) at 20 weeks, and the maternal weight gain between 20 and 36 weeks. The Indian mothers had the lowest mean weight at 20 weeks (57·4 kg) and the West Indian mothers the highest (64·4 kg). The mean maternal weight index and weight gain were very similar in all ethnic groups. Despite their increased weight at 20 weeks the lowest mean birthweight occurred in the West Indians (3148 g) with the highest in the Europeans (3313 g). A low mean birthweight was related to a low weight at 20 weeks in all groups, but the reduction was higher in the groups with the highest overall mean birthweight (e.g. the European group). Failure to gain more than 3 kg between 20 and 36 weeks had little effect on either the birthweight or the neonatal ponderal index in any group except in the Europeans where there was a reduction in both.

The diagnostic value of pregnancy-associated plasma protein A (PAPP-A) measurements in ectopic gestation by A. M. Nysenbaum, H. K. Poulsen, J. G. Westergaard, A. E. Bolton, B. Teisner, J. G. Grudzinskas and M. J. Sinosich. Departments of Obstetrics and Gynaecology, Odense University Hospital, Odense, Denmark, The London Hospital, London, UK, The Royal North Shore Hospital, NSW Australia, Division of Biochemistry, NE London Polytechnic, London, UK

During a 6-month period all 115 women admitted with the tentative diagnosis of ectopic pregnancy were included in a prospective study. The following groups of patients were identified: group A, 60 women who were not pregnant; group B, 28 women who had an intrauterine pregnancy, and group C, 27 women who had ectopic pregnancy. In group B, spontaneous abortion occurred in 12 of the 28 patients (group B_1), whereas in the remaining 16 patients (group B_2) the pregnancy continued without obvious complications. Using a specific RIA (detection limit 5 ng/ml) circulating PAPP-A was not detected in group A. Serum PAPP-A levels in group B_2 were within the normal range. By contrast, only one woman in group B_1 had serum PAPP-A concentration above the 10th centile, whereas the PAPP-A levels in five women were below the detection limit. In patients with ectopic gestation (group C), circulating PAPP-A was not detected in 50% and was below the 10th centile in the remainder. These data suggest that the synthesis of PAPP-A is severely compromised both in ectopic gestation, and before spontaneous abortion, and that PAPP-A measurements may be of diagnostic value in these conditions.

Protein secretion by the endometrium and decidua during early pregnancy by J. O. Drife, M. W. Hales & S. C. Bell. Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Bristol

Although proteins secreted by the trophoblast (e.g. hCG and hPL) are well studied and clinically useful, little is known about proteins secreted by the endometrium and decidua of early pregnancy. We have attempted to determine whether these maternal tissues synthesize and secrete proteins which may be of value in assessing the role of the endometrium during pregnancy. Synthesis and secretion of proteins has now been examined in 52 specimens of endometrium obtained from therapeutic termination of 6–12 week pregnancies, by incubating *in vitro* with ^{35}S-methionine and subsequent analysis of radiolabelled proteins by 1D and 2D gel electrophoresis and fluorography. At least 17 polypeptide species were secreted by these tissues *in vitro* and we observed a striking alteration in the rates of secretion of two proteins, endometrial protein 14 (EP14) and endometrial protein 15 (EP15), between weeks 6 and 12. Secretion of EP14 increases as secretion of EP15 falls, and we suggest that the secretion of EP15 may be associated with secretory endometrium and EP15 with decidual tissue. These endometrial proteins may provide useful markers for studies of the endometrial response in normal implantation, and of the possible involvement of abnormal endometrial differentiation in infertility and pregnancy disorders.

Obstetric antecedents of neurodevelopmental disability by D. J. Taylor, P. W. Howie & C. Drillien. Department of Obstetrics and Gynaecology, Ninewells Hospital and Medical School, Dundee DD1 9SY, Scotland

All children born in Dundee during 1974 and 1975 were screened for neurodevelopmental disability at 2, 5, 9, 15 months and 2 and 3 years of age. A total of 322 singleton children with various forms of disability have subsequently been followed until 7 years of age. We have undertaken a case-controlled investigation of the maternal, fetal, antepartum, intrapartum and neonatal factors associated with neurodevelopmental disability in 300 (93·2%) of these singleton children (index group). Two contemporaneous normally developed children were chosen for each child with disability (control group). Comparing the controls with index group, low social class was associated with mental retardation ($P<0{\cdot}05$), global delay ($P<0{\cdot}001$), speech delay ($P<0{\cdot}05$) and behaviour disorder ($P<0{\cdot}05$), but not with the physical disorders of cerebral palsy and motor delay. With the exception of cerebral palsy, strong statistical associations were found between all categories of disability and the following obstetric antecedents: severe hypertension ($P<0{\cdot}01$), unclassified antepartum haemorrhage ($P<0{\cdot}001$), preterm uterine activity and subsequent term delivery ($P<0{\cdot}001$). These antepartum complications remained statistically more frequent in the index group than the control group after a correction had been made for social class. In contrast, cerebral palsy was not associated with antepartum complications, but with fetal tachycardia during labour ($P<0{\cdot}05$). Our results suggest that the origins of neurodevelopmental disability may, in many cases, occur during pregnancy and delivery.

Transvesical ultrasound directed oocyte recovery by R. K. Goswamy, J. H. Parsons, V. Sharma, A. F. Riddle, M. W. Booker, L. Wilson, P. Vaid, P. Matson, M. I. Whitehead & S. Campbell. King's College Hospital, London and B. Mason, H. West, S. Avery, A. Holloway, D. Brison. Dr Mason's Clinic, London

For in-vitro fertilization and embryo transfer to realize their full potential in the treatment of infertility, the techniques need to be adapted, simplified and made less expensive. Only then will they become more widely available. To simplify and reduce costs of treatment, we have developed a programme based entirely on outpatient procedures. Ovarian stimulation and follicular development have been monitored solely by ultrasound. Thirty-four hours after administration of hCG, all follicles >15 mm mean diameter have been aspirated by transvesical ultrasound-directed needle aspiration. Patients have been allowed home 2 h later. Fertilized ova have been replaced 48 h after the aspiration, each patient resting for 1–2 h before returning home. The procedure was attempted on 215 occasions and a total of 513 oocytes retrieved. At least one egg was recovered on 184 occasions (85%); and more than one egg was collected on 132 occasions (61%). A total of 113 women have had embryos transferred (52%) and 10 pregnancies have been achieved.

The prognostic value of seminal analysis in infertility by C. M. A. Glazener, N. Kelly, C. Coulson, P. A. Lambert, M. Watt, R. A. Hinton, B. Rosevinck, J. David, J. Weir, J. S. Cornes & M. G. R. Hull. Department of Obstetrics and Gynaecology, Bristol Maternity Hospital, Bristol

The predictive value for fertility was determined for each variable, and all combinations of variables, measured by standard seminal analysis [sperm count, density, motility (% progressive) and morphology (% normals)]; for morphology by vital staining; and for in-vivo penetration of cervical mucus (by the postcoital test, PCT) in fertile couples in whom ovulatory, tubal and coital causes of infertility were excluded. Fertility was expressed by the cumulative conception rate (CCR) after 18 months, calculated using life-table analysis. The seminal value above which fertility increased no further was taken in to the 'threshold value' for fertility. In treated oligomenorrhoeic women (assumed to have average husbands) the best seminal predictor of fertility was the motile normal sperm density (i.e. % motile × % normal × sperm density: MNSD) $\geq 4 \times 10^6$/ml (CCR 87%, *vs* 38% when MNSD $< 4 \times 10^6$/ml, $P<0{\cdot}001$). In normally menstruating infertile women, the best seminal predictor was the MSD (% motile × sperm density) $\geq 5 \times 10^6$/ml (CCR 55%, *vs* 24%, $P<0{\cdot}001$) but this failed to distinguish a few couples with a low proportion of normals in addition. Therefore the generally most useful variable seemed to be the MNSD $\geq 4 \times 10^6$/ml (CCR 57%, *vs* 30%, $P<0{\cdot}001$). Vital staining was unhelpful. The best predictor of all was a positive PCT (forward progressing sperms) (CCR 56%, *vs* 15% for a negative PCT, $P<0{\cdot}001$). Furthermore, fertility was equally good with a positive PCT whatever the MNSD, but with a negative PCT, the MNSD provided further discrimination (CCR 23%, *vs* 6%, $P<0{\cdot}05$). In conclusion, standard semen analysis was of poor predictive value in the investigation of infertility. Low values, however, provided stronger indication of poor fertility when combined with a negative PCT. The PCT proved to be the single most useful investigation.

Estimation of the frequency of pulsatile luteinizing hormone (LH) release by the time series analysis by A. P. Murdoch. Department of Obstetrics and Gynaecology, University of Newcastle Upon Tyne. P. J. Diggle. Department of Statistics, University of Newcastle Upon Tyne. W. Dunlop. Department of Obstetrics and Gynaecology, University of Newcastle Upon Tyne. P. Kendall-Taylor. Department of Medicine, Royal Victoria Hospital, Newcastle Upon Tyne

Infertility treatment using pulsatile luteinizing hormone releasing hormone has shown the importance of pulsatile LH release but so far little attention has been paid to the determination of the normal LH pulse frequency. The significance of an alteration of pulse frequency in other pathological conditions has yet to be explored. Existing methods of determining the 'frequency' of the pulsatile release of LH are unsatisfactory since they actually estimate the incidence of statistically definable pulses in a given time period rather than predict the true frequency of the pulses. Statistical methods of 'time series analysis', in particular 'spectral analysis', have been applied in this study. This analysis is a decomposition of the total variation in the series into its hormonic components and hence enables us to estimate the true frequency of the LH pulses. Twelve normal women aged between 18 and 39 years were studied during the early follicular phase of the menstrual cycle. An indwelling intravenous cannula was inserted at 08.30 hours and samples for LH determination were taken every 15 min for 6 h. In six women the study was repeated using a sampling interval of 5 min. No consistent pattern emerged from the initial study using a 15-min sampling interval but a mean pulse frequency of 60 min was detected. The 5-min sampling interval data gave much clearer individual results. Low frequency harmonics (perhaps reflecting a diurnal variation) were seen in four of the six subjects. A dominant harmonic range (51–120 min) was found in five of the six subjects. In one subject, rapid oscillations (13·3 and 20 min) were detected in addition to a dominant harmonic of 72 min and a low frequency harmonic. Comparison of repeat studies on four women at the same stage of different menstrual cycles found no significant difference in their spectral patterns. This method of analysis enables the true pulse frequency to be determined for the first time. A new observation of superimposed harmonic components of LH pulsatility is revealed. Accurate comparison of pulse frequency between and within individuals can be made.

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CORRESPONDENCE

Neural-tube defects and vitamins: the need for a randomized clinical trial

Dear Sir,

We were interested to read the article by Professors Wald and Polani [*Br J Obstet Gynaecol* (1984) **91,** 516–523]. They have a perfect right to defend the Medical Research Council's randomized clinical trial of vitamins for prevention of neural-tube defect (NTD) recurrences if they feel it needs to be defended. We regret, however, that the defence is based principally on a biassed selection of data from our studies and a hypothetical prediction based on questionable premises. The following comments follow the order of their paper.

(1) *Blood levels of vitamins and NTD.* Deficiency of one nutrient is indeed usually associated with deficiency of others and we have never suggested that the protective effect of multivitamin supplements is attributable to a single vitamin. We showed deficiencies in early pregnancy associated with NTD but not associated with congenital heart disease (Smithells *et al.* 1976) which indicates a degree of specificity.

(2) *Experimental animal work.* This is not particularly relevant to the need for human studies, but if it is to be quoted it should be reasonably comprehensive. Although it is true that most animal work on folic acid deficiency has incorporated antagonist drugs, Giroud & Lefebvres (1951) and Giroud *et al.* (1952) induced deformities in rats using a deficient diet plus succinylsulphathiazole to suppress intestinal synthesis, but no antagonist drug. Moffa & White (1983) were able to reduce the birth prevalence of NTD in a genetically predisposed strain of hamsters by giving folic acid supplements.

(3) *There is also no suggestion that countries in which the average diet is likely to be lacking in vitamins have unusually high rates of NTD.* Which countries are these? What data are available about NTD rates? In countries where protein and calories are in short supply, vitamin C, folic acid and sunshine are usually plentiful (Naismith 1983). Furthermore, the genetic constitution of people in these countries is quite different.

(4) *Social class bias.* The authors quote figures from our first cohort only, and include partially supplemented mothers. Using the same groups and quoting from our first and second cohorts combined (Smithells *et al.* 1983), the sentence would read, 'Of 27 women who had NTD pregnancies, 10 (37%) were of high social class compared with 388/994 (39%) of those who did not have affected pregnancies'. The difference in recurrence rates between supplemented and unsupplemented women in social class III alone in the combined cohorts is significant, in spite of the fact that this includes all three recurrences in supplemented mothers but only 15 of 24 in unsupplemented mothers.

(5) *Preceding abortion.* The authors have again quoted from the first cohort only, this time excluding partially supplemented mothers. Using the same groups from the combined cohorts (Smithells *et al.* 1983) the sentence would read, '[More] women whose preceding pregnancy did not end in a spontaneous abortion took the supplements than did women who did have such a history, 395/834 (47%) compared with 59/139 (43%)'. The difference is not significant. In study pregnancies with known outcome immediately preceded by spontaneous abortion, NTD recurrences were 0/52 in fully supplemented and 7/77 (9·1%) in unsupplemented women ($P<0·03$). In study pregnancies *not* preceded by abortion (spontaneous or therapeutic) the corresponding figures were 2/322 (0·6%) and 16/402 (4·0%), $P<0·003$ (Wild *et al.* unpublished observations

(6) *Patient selection.* There are several references to patient selection, and to 'the reasons that influenced the selection into supplemented and unsupplemented groups'. One of the criteria for admission to the trial, which is explicit in our publications, is that the mothers must not be pregnant. Of all *eligible* mothers (i.e. non-pregnant) in our first and second cohorts, the few who declined to take part are excluded from the study. A number of mothers who were pregnant when first ascertained, and were therefore

unsupplemented in that pregnancy, were supplemented in a subsequent pregnancy.

(7) *The Dublin experience.* The authors quote the differing NTD recurrence rates in four Dublin maternity units and say these are 'quite unexplained'. This is true, but at a workshop attended by Professor Wald (Dobbing 1983) the interesting fact emerged that the policy at the hospital with the lowest recurrence rate was to send all mothers home after delivery with 50 days' supply of folic acid and iron, while that at the hospital with the highest rate was to stop supplements at delivery.

(8) *'Although there is at present no evidence that any of the extra vitamins used in the NTD intervention studies will cause harm, there is also no evidence that they are acceptably safe'.* Our own studies have included an active search for harm in the offspring of vitamin supplemented mothers and have so far revealed none. Absolute safety cannot be proved. The suggestion of possible harm from doses of vitamins approximating to recommended daily allowances (as used by us) is difficult to reconcile with the decision to use an 11-fold higher dose of folic acid in the MRC trial.

(9) *The hypothetical model.* In the footnote to Fig. 1, four assumptions are made: (i) That vitamin supplements prevent 50% of NTD recurrences. Any figures can be used in a hypothesis, but our data (allowing for imperfections) suggest that this is likely to be over-conservative. (ii) All women accept selective abortion. This ignores the fact that many women who would not accept abortion try to avoid further pregnancies. (iii) Vitamin supplements cause an extra 0.2% malformations. There is no evidence to justify this assumption. (iv) Half the non-NTD defects would result in handicap. We seriously question the validity of this. However, even if the assumptions are accepted, with the conclusion that the same number of handicapped children would be born to supplemented as to unsupplemented mothers, twice as many unsupplemented as supplemented mothers (90 cf. 45) would have their pregnancies terminated. This does not seem to trouble Professors Wald and Polani as much as it troubles us.

The model relates to '4000 women in Britain' and is therefore possibly inappropriate for the MRC trial which will include mothers in Australia, Israel, Hungary and Canada as well as in Britain. The eventual aggregation of these diverse groups for the purposes of analysis must raise some difficulties.

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Authors' reply

Dear Sir,

Nothing in the accompanying letter by Professor Smithells and his colleagues alters the conclusion that the data on the effect of taking extra vitamins around the time of conception are open to more than one interpretation and, in our view, the evidence does not exist to justify the routine use of such a regimen in clinical practice.

We do not consider our opinion to be based principally on a biased selection of data from their study. We used data from the report relating to their first series of patients since the second was simply an extension of the first, and for the reasons given in our paper, no amount of additional data collected in the same way can avoid the same biases. Our demonstration of bias being introduced through differences in the social class distribution of the suplemented and unsupplemented women holds regardless of whether data on the partially supplemented women are included or excluded. Similarly, our example of bias being introduced in relation to whether the women had had a history of miscarriage in the preceding pregnancy is evident whether or not the partially supplemented women are included.

It is true that since the data of Smithells and his colleagues are presented in various ways, judgment is required as to which particular analysis of the results to choose. In general, the different analyses do not materially alter the conclusion, but the results relating to the social class of the women are different in the first and second series. In the first series, as one would expect, high social class is associated with a low risk of a neural-tube defect (NTD). In the second series, surprisingly, the opposite is found, and since this is contrary to our knowledge of the epidemiology of neural-tube defects, we have an additional reason to believe that our decision to exclude data on social class from the second series was correct.

Allowance for the confounding effects of social class is always imperfect. Even restricting the analysis of NTD recurrence risk to women in social class III does not mean that like is being compared with like, since even within this social class category (which includes nearly 50% of the general population), there will be women from a wide variety of backgrounds and lifestyles. Therefore, any differences observed between supplemented and unsupplemented women could still be due to differences between the women that had nothing to do with the vitamins *per se*, but were nevertheless of the same type as those indicated by social class. In other words, since social class is such a crude indicator of the actual factors involved, stratifying results by social class cannot eliminate confounding due to social class.

The geographical variation in the birth prevalence of neural-tube defects is illustrated in Table 10.1 in the book by Elwood & Elwood (1980). For example, in Bombay, the prevalence of anencephalus was 1·89 per 1000 births, lower than in Birmingham (2·41 per 1000 births) where vitamin deficiency is surely less common; for spina bifida, the figures were 1·08 and 2·36 respectively. The only community cited in the Table with a relatively high rate of neural-tube defect in an under-developed country is Alexandria. It is certainly possible to propose various genetic–environmental interactions that could explain data that, on their face value, tend to weight against the hypothesis that a simple dietary deficiency, such as vitamin lack, is an important cause of neural-tube defects. But without being able to identify the genetic factor, such speculation is unhelpful.

The suggestion that the differing NTD recurrence rates in the four Dublin maternity hospitals were related to postpartum folic acid supplementation is speculative. No information is available on when in relation to the supplementation the pregnancies occurred, or whether the supplementation was actually taken.

The question of the dose of folic acid is discussed in our paper. If folic acid is effective, it may well be more effective using a dose higher than that used by Smithells and his colleagues. Indeed, the data from Laurence *et al.* (1980, 1981) though based on small numbers, suggest that this may be the case. In the MRC Study the intention is to maximize the opportunity of identifying a prophylactic effect, if one in fact exists.

In the example we used in our paper, both the benefits and the risks were necessarily assumed, since neither are known. Our purpose was to show that, using reasonable assumptions, a relatively low rate of serious adverse effects could easily outweigh the benefit which a vitamin supplementation regimen may have. This conclusion would still hold if alternative reasonable assumptions were made. As we stated in our article, it is important not to overlook the distress associated with a positive antenatal diagnosis and termination of pregnancy. But the impossiblity of quantitatively comparing the suffering of a handicapped child and the distress from the termination of a fetus affected by an open neural-tube defect dictated that we restrict our outcome measure to estimates of the number of handicapped children expected in the vitamin group and in the control group. The purpose of this trial is to establish whether either of these outcomes can be avoided without a greater risk of other adverse effects.

There should be no difficulty in comparing the results from centres in different regions and countries since comparisons will be made between supplemented and unsupplemented women within each centre and the differences aggregated for all the centres. If there are differences in the value of vitamin supplementation in different countries the MRC study is well suited to identifying them.

There is no disagreement that vitamin lack is a *possible* cause of neural-tube defects. What is at issue is whether we can reach a judgment simply on the basis of this possibility or whether there is an obligation to exclude other reasonable explanations for the existing results. Smithells and his colleagues have not been able to show that the alternative explanation (that the women who took the vitamin supplements were in any case at low risk of NTD) is so unlikely as to be discounted. We do not argue that randomized studies are always necessary. They are not. But in this instance the doubt and its implications are such as to make a randomized study essential.

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Consumers' attitude to obstetric care

Dear Sir,

I write in response to the article by Morgan *et al.* [*Br J Obstet Gynaecol* (1984) **91**, 624–628].

While I am in absolute agreement with the authors as to the need for more systematic and scientific assessment of the attitudes of 'consumers', there seem to me to be a number of quite serious problems with this particular survey and its interpretation. I would list some of the main ones as follows:

(1) Mention is made in the summary of the fact that the response rate in the 1-year follow-up was 63%. This is not only disappointing, but, rather more importantly, we are given no information as to how the social and obstetric characteristics of the non-responders compare with those of the responders. That the authors do not have data from more than a third of the original 1000 mothers puts serious limits on the generalizability of the results presented in the paper.

(2) The mothers whose views are conveyed in the paper are those who had a vaginal delivery of a live child. A significant minority of mothers are thus not represented.

(3) Statistics, as we all know, may be construed to tell many stories. Thus, for example, Morgan and her colleagues dub 19% of the survey responders 'only' a few. Yet if 1 in 5 mothers think mother–child bonding is influenced by labour and delivery events, this is surely an interesting and potentially important fact.

(4) The validity of the paper's general conclusion, that most of the attitudes revealed by the survey were more in agreement with 'the established medical view' than with 'the views of natural-childbirth groups' of course depends partly on how these two (opposing ?) sets of views are defined. (I do not know, for instance, where forgetting, versus not forgetting, the pain of labour would fit into this polarity.) It does not seem to me to be possible to define the views of doctors or of natural-childbirth advocates with-

out asking a respresentative sample of each what they think; and I can find no reference to such an exercise in the paper.

Aside from this, many of the data presented in the paper appear to be at odds with the broad conclusion that mothers agree with doctors rather than with protagonists of natural childbirth. For example, 61% of mothers thought a sympathetic midwife more important than other forms of analgesia and 19% (1 in 5, again) did not consider 'monitoring machinery' reassuring. I cannot find any evidence in the paper for the conclusion that mothers 'roundly rejected' the equation of medical attention in labour with 'unwanted interference causing childbirth to be seen as an illness'. They do not appear to have been asked.

(5) The references to the paper contain little in the way of recognition of the very large volume of medical sociological work that has been carried out over the last 25 years in the area of patients' attitudes towards, and the experiences with, their medical care. Moreover, there is no acknowledgement of the substantial methodological problems involved in the assessment of patient satisfaction.

All this is a great pity, since many of us working in this field would certainly support Morgan and her colleagues' appeal for the substitution of hard data for soft media (and other) speculations.

Ann Oakley
National Perinatal Epidemiology Unit
Radcliffe Infirmary
Oxford OX2 6HE

References

Morgan, B. M , Bulpitt, C. J., Clifton, P. & Lewis, P. J. (1984) The consumers' attitude to obstetric care. *Br J Obstet Gynaecol* **91**, 624-628

Authors' reply

Dear Sir,

We are grateful for the interest shown in our paper by Dr Oakley. She suggests, however, that our statement, 'some attitudes were in broad agreement with the view of natural-childbirth groups but more were in agreement with the established medical view' is not correct.

Some of the more important tenets of the modern obstetric practice were supported by the majority of the mothers. Only 9% thought they should not have so much medical attention in pregnancy and labour, 19% thought that monitoring machinery on the labour ward was not reassuring and 16% thought that home deliveries ought to be encouraged.

Some of the well publicized views of natural-childbirth lobbies were supported by many mothers: 45% felt that pain was a necessary part of the emotional experience of labour, 70% thought that the mother soon forgets the pain of labour and 61% thought that a sympathetic midwife was more important than pain relief. However, the view that the mother–child bond is increased by pain of labour or by how she felt in labour, or that the child's personality is affected by its birth, were not held be most mothers.

Dr Oakley also rightly worries that the 37% of non-respondents would have reported differently. In fact, just over 100 of these non-respondents had simply moved house and were not traced. The 632 women who did respond are a large cohort of recently delivered mothers who expressed their views.

The important fact that, although in the minority, 1 in 5 mothers thought that mother–child bonding was affected by labour is cited by Dr Oakley. In fact, only 5% of mothers strongly agreed with this view, 14% agreed, 48% disagreed and 18% strongly disagreed. Assuming that half the non-respondents agreed with this view, 29% of the 1000 mothers would have agreed and 53% disagreed. It is more likely that 1 in 5 would have agreed, and impossible for the majority to have agreed.

We excluded from our study the mothers of one stillborn baby and one neonatal death on humanitarian grounds.

We have tried to report our data without prejudice or statistical bias in this difficult field of mothers' opinions.

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London School of Hygiene and Tropical Medicine

British Journal of Obstetrics and Gynaecology
February 1985, Vol. 92, pp. 190–192

BOOK REVIEWS

Reproductive Ethics Prentice-Hall Series in the Philosophy of Medicine by Michael D. Bayles. Prentice/Hall International, Hemel Hempstead, 1984, 141 pages, £9.45

This clearly argued and well-referenced book provides a valuable addition to the Prentice Hall series on philosophy of medicine. The topics dealt with are to some extent predictable—contraception, sex selection, screening, abortion, neonatal care, genetic experimentation—but an unusual feature is the addition of choices in childbirth (home, hospital, special clinic). The whole book is slightly biased toward a North American readership (especially the chapter on childbirth), but the issues are so fundamental that any reader will find its blending of case material, ethical analysis and discussion of legislative measures useful and interesting. The book ends with a selection of additional cases and 'scenarios' which raise questions which are left to the reader to answer. The arguments in the book proceed from certain assumptions, notably that 'freedom is a basic value of rational persons' and that rationality is itself the chief criterion for determining moral choice. Arguments against the presumption of freedom are accepted by Bayles only when freedom can be shown to conflict with what he describes as 'rational desires'. Not surprisingly, this starting point leads to a number of liberal conclusions about the moral issues raised: abortion on request should be permitted up to 28 weeks gestation (and later in some circumstances); active euthanasia of defective neonates is not ruled out; surrogate motherhood should not be legislated against; the extremes of genetic experimentation are seen as crossing a boundary, where freedom ceases to be absolute, but most other new developments in reproductive medicine are viewed positively. Those who practice in the field of obstetrics may find the approach of this book too philosophically technical in places (clinicians are often impatient with the jargon of *other* disciplines!) But the arguments merit serious attention, not least because they are commendably brief and to the point. Many ethical theorists would quarrel with Bayles' conclusions, viewing his stock of ethical premises as too meagre for an adequate consideration of human wellbeing. But, whether one agrees with it wholly or not, this book should not be overlooked by anyone concerned with social policy or personal decision making in reproductive medicine.

A. V. Campbell

Illustrated Textbook of Gynaecology by E. V. Mackay, N. A. Beischer, L. W. Cox & C. Wood. W. B. Saunders Co, Australia, 1983, 496 pages fully illustrated with photographic plates, £11.75

Fashions in undergraduate teaching have changed substantially in this country during the past 15 years. For better or for worse, the new doctor is nowadays seen as an amorphous mass of totipotent tissue rather than as an embryonic specialist, already fully informed at graduation. Things are different, it appears, in Australia. Here is a textbook which places a pleasantly archaic emphasis upon the detailed practicalities of gynaecology rather than upon vague and woolly principle. This makes for stimulating reading but may be prejudical to widespread use of the book in British medical schools. Illustrations abound; all are black and white and many are grouped so as to depict different facets of well-chosen clinical cases. Sometimes however enthusiasm overwhelms sobriety. No less than 10 basal body temperature cycles are reproduced within four pages of text (plasma progesterone estimation merits only a paragraph) and both low- and high-power photographs are provided of ferning in cervical mucus. There is rather more emphasis upon operative gynaecology than is usual in modern British teaching, and a short chapter on breast disorders is included. Most chapters commence with a brief overview of the subject to be discussed. While this is often valuable, there are occasions, as in the chapter on cell structure and function, when virtually no information is provided and the device becomes pointless. The inclusion of a chapter entitled 'Relative incidence of gynaecological disease' is a laudable idea; unfortunately substantial quantities of totally unreferenced epidemiological data are provided, so that it is impossible to assess either the accuracy of the material or its relevance to gynaecological practice elsewhere. Omission of references is a deliberate policy. This results in a style which, being expository rather than inductive, will not be acceptable to all tastes. Clear writing and profuse illustration at a bargain price will no doubt secure for this book substantial popularity. Nevertheless, it is likely to have relatively short shelf life and is unlikely to stimulate a spirit of enquiry among its readers.

W. Dunlop.

Clinics in Obstetrics and Gynaecology Vol 11/No 1 Gynaecological Pathology: Advances, Perspectives and Problems edited by H. Fox. W. B. Saunders, London, 1984, 293 pages with figures and tables, £12.50

Thirteen chapters are devoted to 'Advances, Perspectives and Problems', in gynaecological pathology. Informed discussion on a variety of subjects, many of which represent classical diagnostic 'grey areas', are presented. Sections of immunocytochemistry and electron microscopy together with a useful chapter on quantitative methods are followed by a well-balanced account of sex cord—stromal tumours and an update of trophoblastic disease. The latter includes the less-well-documented 'partial mole' and 'placental site trophoblastic tumour'. The highly controversial subject of vulval dystrophy is dealt with in an acceptable manner, presenting a rationalization of terminology and an interesting aetiological hypothesis. Colposcopic, histological and cytological views on genital tract condyloma are expressed, with observations on possible neoplastic associations. Dealing with endometrial carcinoma, important distinctions are drawn between this and the sometimes confused metaplasias and hyperplasias; a guide to the assessment of myometrial invasion is advanced. The role of the endometrium in infertility and subfertility and the value of endometrial biopsy in these circumstances precedes current views on dysfunctional uterine bleeding. The importance and diagnostic credibility of 'micro-invasive' carcinoma of the female genital tract is examined, followed by a plea for close clinico-pathological co-operation in the diagnosis and management of borderline ovarian tumours; definitions, therapy and survival are discussed. Finally, there is an updated review of the pathogenesis of endometriosis. Because of the proportion of the laboratory work load occupied by gynaecological pathology added to the problematic nature of the subjects covered, this book is a necessity for histopathologists and a highly recommended publication for clinicians.

J. O. W. Beilby

Clinical and Diagnostic Procedures in Obstetrics and Gynecology Part B Gynecology edited by E. Malcolm Symonds & Frederick P. Zuspan. Marcel Dekker, New York, 1984, 472 pages with figures and tables. SWFr 145

This is the second of two useful volumes which offer practical advice about simple procedures in obstetrics and gynaecology. Once again, the editors have selected an international group of expert authors, so that the book will be of interest throughout the English-speaking world. The subject-matter is diverse, ranging from hypnosis for pelvic pain to minilaparotomy for sterilization. Inevitably there are substantial differences between chapters in approach, style and content but there is much that is of value here. It would be invidious and unprofitable to itemize all of the contributions to this book. Particularly noteworthy are clearly written chapters by Jordan on the treatment of cervical disease, by Uchida on sterilization and by Schmidt on laparoscopy. The investigation and treatment of urinary incontinence is covered in some detail. Seventeen of the 27 pages allocated to the topic of 'Urethroscopy with carbon dioxide cystometrogram' are concerned with the physiology of the lower urinary tract. Thereafter a brief review of the standard British approach to urodynamic investigation is followed by a lengthy 'Overview of urinary stress incontinence' a condition which, it is suggested, is best treated by anterior colporrhaphy. There is a comprehensive section covering the diagnosis and treatment of cervical disease. Separate chapters are allocated to menstrual extraction, and to techniques of termination of pregnancy during both the first and the second trimesters. The last of these deals only with techniques widely used in the United States with the result that no mention is made of prostaglandins of the E series, nor of their extra-amniotic administration. A comprehensive chapter entitled 'Anesthesia for the outpatient' is probably also of more value to a transatlantic readership, but subsequent accounts of hysterosalpingography and hysteroscopy are succinct and interesting. Most of these reservations are minor, however. The book is well produced and clearly illustrated in black and white. It can be recommended as a readable account of commonly used procedures and would be of value as a supplementary text to those preparing for the MRCOG.

W. Dunlop

Books received some of which may be reviewed at a later date

Gynecologic Cancer Contemporary Issues in Clinical Oncology Volume 2 edited by Arlene A. Forastiere. Churchill Livingstone, Edinburgh, 1984, 307 pages, illustrated, £36.00

Human Alkaline Phosphatases Progress in Clinical and Biological Research. Volume 166 edited by Torgny Stigbrand & William H. Fishman. Alan R. Liss Inc., New York, 390 pages with figures and tables, £37.00

The Biochemical Effects of Drugs in Pregnancy Volume 1: Drugs Active on the Nervous, Cardovascular and Haemopoietic Systems by A. Onnis & P. Grella. Ellis Horwood Ltd, Chichester, 1984, 396 pages with tables, £45.00

An Introduction to Recombinant DNA by Alan E. H. Emery. John Wiley & Sons, Chichester, 1984, 223 pages, with figures and tables, £6.75

Clinics in Obstetrics and Gynaecology Vol II/No 2 The Small Baby edited by P. W. Howie & N. B. Patel. W. B. Saunders Company, London, 1984, 547 pages with figures and tables, £12.50

Maternal Fetal Medicine edited by Robert K. Creasy & Robert Resnik. W. B. Saunders Company Ltd, Philadelphia, 1984, 1147 pages fully illustrated, £95.00

Practical Colposcopy Second Edition by Rene Cartier. Laboratoire Cartier, Paris, 1984, 310 pages with more than 800 colour plates, no price given

Atlas of Gynaecological Diagnosis by Abdel Fattah Youssef. Churchill Livingstone, Edinburgh, 1984, 179 pages fully illustrated with coloured plates, £17.00

Ovulation and its Disorders (Studies in Fertility and Sterility) edited by W. Thompson, R. F. Harrison & J. Bonnar. MTP Press Ltd, Lancaster, 1984, 179 pages with figures and tables, £29.95

Thermal Assessment of Breast Health Proceedings of an International Conference, Washington, July, 1983, edited by M. Gautherie, E. Albert & L. Keith. MTP Press Ltd, Lancaster, 1984, 288 pages illustrated, £39.95

Nutrition and Feeding of Infants and Toddlers edited by Rosanne B. Howard & Harland S. Winter. Little Brown and Co, Boston/Toronto, 1984, 476 pages with figures and tables, US$43.40

Human Sexuality in Nursing Care by Jean Glover. Croom Helm Ltd, Kent, 1984, 162 pages, paperback £6.95

Pregnant Women at Work edited by Geoffrey Chamberlain. The Royal Society of Medicine and The Macmillan Press Ltd, London, 1984, 301 pages with figures and tables, hardback £32.00, paperback £15.00

Psychological Aspects of Genetic Counselling edited by Alan E. H. Emery & Ian Pullen. Academic Press Inc, Florida, 1984, 236 pages with figures and tables, US$32.00, £19.00

Medical Management of Endometriosis edited by Jean-Pierre Raynaud, Tiiu Ojasoo & Luciano Martini. Raven Press, New York, 1984, 307 pages, £47.00

High-Risk Pregnancy and Delivery edited by Fernando Arias. Blackwell Scientific Publications, Oxford, 1984, 394 pages with figures and tables, £38.00

Suicide in Pregnancy edited by George J. Kleiner & Wilma Markus Gleston. John Wright PSG Inc., Bristol, 1984, 213 pages with figures and tables, £22.50

Alcohol and the Fetus. A Clinical Perspective by Henry L. Rosett & Lyn Weiner. Oxford University Press, 1984, 220 pages with figures and tables, £20.00

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All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution; major changes will be agreed with the author(s)

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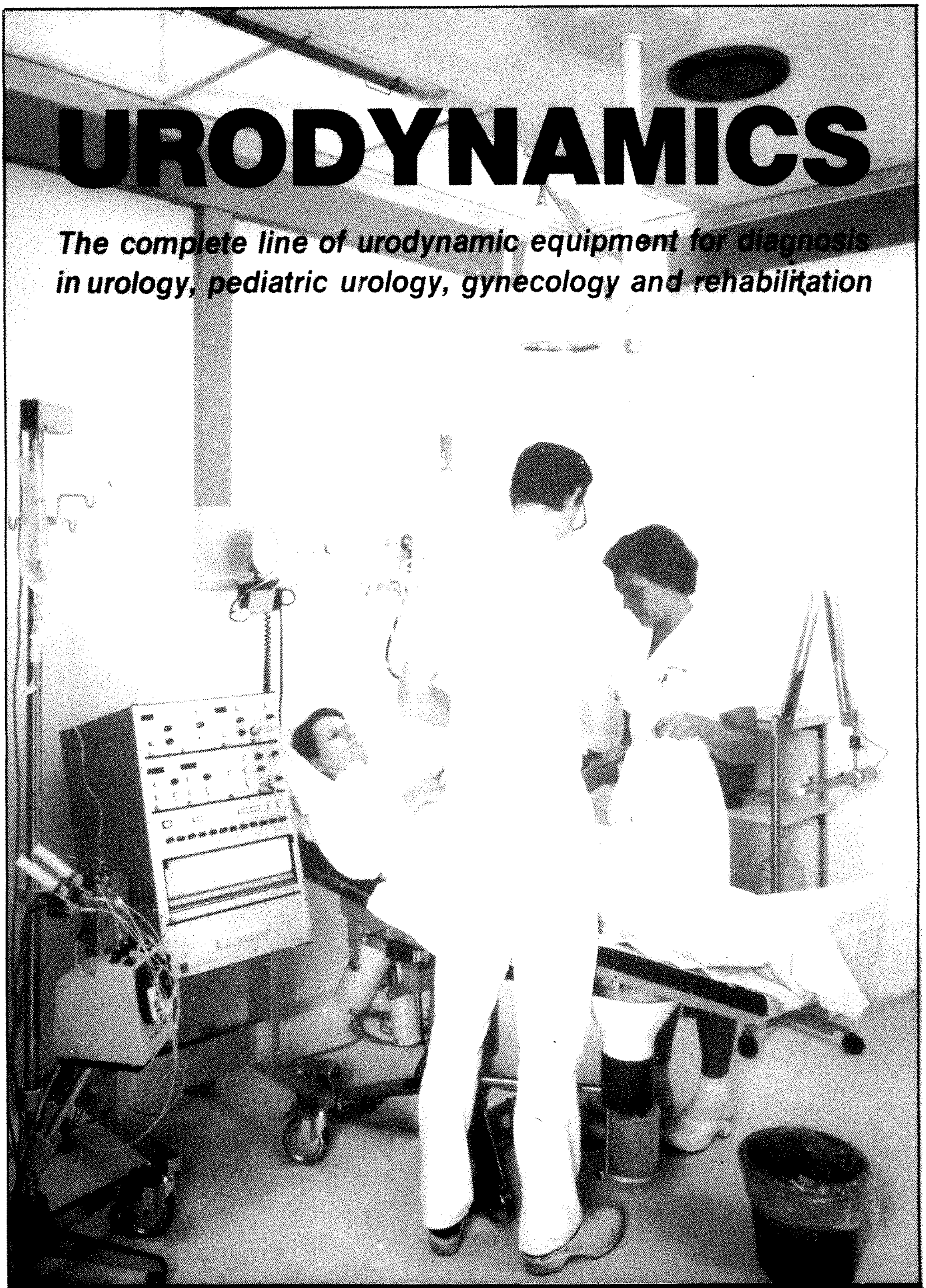
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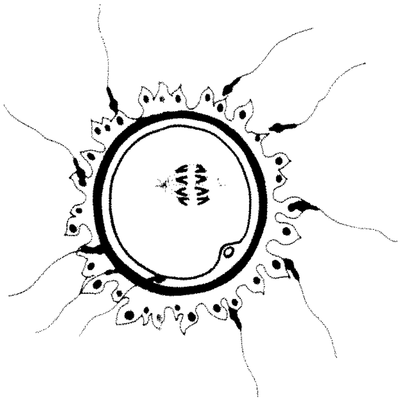

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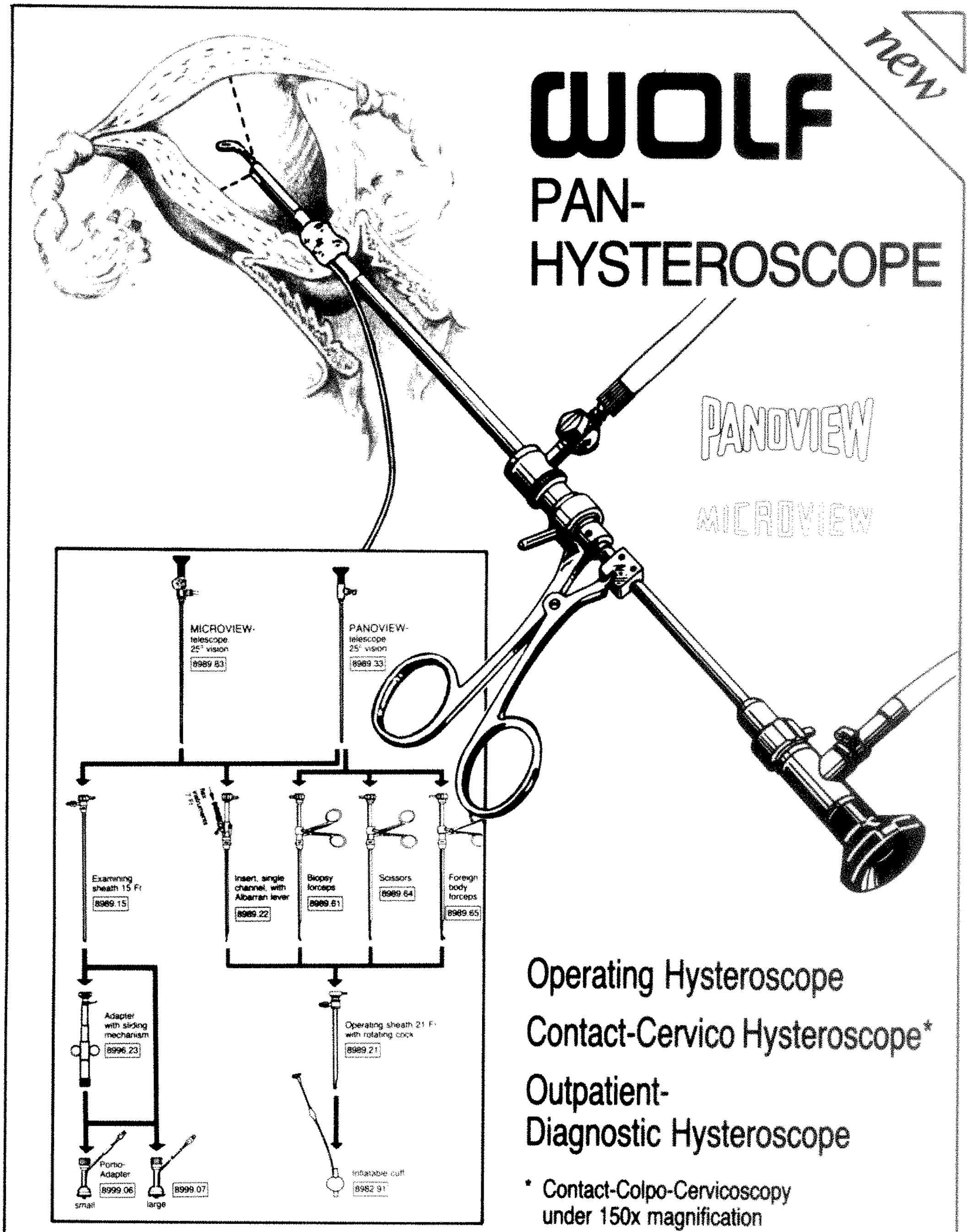

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COMMENTARY

Rubella—continuing problems

Despite the availability of safe and effective attenuated rubella vaccines and sensitive laboratory tests for rubella antibody screening and diagnosis, most clinical virologists continue to receive a large number of queries relating to maternal rubella from their obstetric and general practitioner colleagues.

Perhaps the most frequent query relates to the interpretation of conflicting results of rubella antibody screening tests carried out in antenatal clinics. Thus, one report may state that the patient is immune, obviating the necessity of postpartum vaccination, whereas a second test in a subsequent pregnancy may report that the patient is susceptible. This confuses obstetricians, creates anxiety among patients and casts doubt on the credibility of laboratory tests.

The test which is most generally used for rubella antibody screening in the UK is the single radial haemolysis test (SRH); it is cheap, simple and reliable and, unlike the haemagglutination inhibition test (HAI), which it has largely replaced, does not give false-positive results. However, false-negative results occur due to the presence of 'blocking factors' in 1–3% of sera.

What concentration of antibody should be acceptable as indicative of rubella immunity? Although it is probable that any concentration of naturally acquired antibody is protective, in that it will prevent viraemia with its attendant risk of fetal infection, this may not necessarily apply to vaccine-induced antibody (O'Shea *et al.* 1983). The presence of relatively low concentrations of rubella antibody is usually responsible for contradictory reports in successive tests. Most laboratories accept a level of 15 i.u./ml as protective although this level is arbitrary and perhaps conservative. There is no difficulty in interpreting reports on patients whose sera have concentrations in excess of 15 i.u./ml (immune); following naturally acquired infection, such levels are likely to persist for periods of at least 18 years, and usually for very much longer, even for life. However, following rubella immunization, about 10% of vaccinees have concentrations of rubella antibody which decline to <15 i.u./ml over a 16–18 year period (O'Shea *et al.* 1982, 1984; Zealley & Edmond 1982). Interpreting reports on sera obtained from patients without detectable rubella antibody who are clearly rubella-susceptible and should be offered rubella vaccination postpartum is also straightforward. Problems tend to arise when sera have antibody concentrations just at, or below, the 15 i.u./ml 'cut-off', since the result may be reported as immune on one, and susceptible on another occasion. This phenomenon may be due either to the concentration of antibody declining between successive tests, or variation in the sensitivity of the test procedure itself. Confusion could, to a large extent, be overcome if laboratory workers ensured that results were not merely reported as '>15 i.u./ml immune' or '<15 i.u./ml susceptible' but were qualified by including appropriate standardized statements in the following terms (Pattison 1982):

(1) SRH—>15 i.u./ml—rubella antibodies present.
Immune. Vaccination not required.

(2) SRH—no antibodies detected.
Susceptible. Vaccination recommended.

(3) SRH—<15 i.u./ml—low level of rubella antibody detected.
Regard as susceptible. Vaccination recommended.

Although all obstetric units have access to a rubella antibody screening service, they must strive to improve delivery of rubella vaccine to rubella-susceptible patients postpartum. Thus, if details of rubella immunity are not displayed prominently in the patient's notes, identification of those who should be offered rubella vaccine may be poor. Some patients may be discharged from hospital rapidly and their general practitioners may fail to offer rubella vaccination at home. Rubella-susceptible patients who miscarry or have ectopic pregnancies may be admitted to gynaecological wards which may not be geared to administer rubella vaccines. A futher error, which may have medicolegal consequences, may arise because the blood of a patient who has been exposed to, or has developed a rubella-like illness, is referred to the laboratory accompanied by a request form for rubella screening with only brief but inadequate details of the patient's rubella contact, or no information at all. In due course, a report, on the lines quoted above, may be returned to the antenatal clinic. Clearly such a report is inappropriate and misleading since patients who are rubella contacts, or have developed an illness compatible with rubella, require a detailed history and usually additional tests on follow-up blood samples to determine whether seroconversion occurs, or if the patient is seropositive, whether antibodies are long standing or of recent duration (eg, tests to detect rubella-specific IgM). In an attempt to obviate this risk, it is a wise precaution to print boldly on request forms for rubella screening: 'This card is not to be used for patients exposed to, or developing, rubella-like illnesses in pregnancy. Whenever possible, a doctor in the virology laboratory should be consulted about such patients.'

It is regrettable that in 1983 there were 419 cases of maternal rubella, a higher number than in all but 2 of the previous 6 years. It is encouraging that recent serological studies have shown that the proportion of susceptible women of child-bearing age is declining. Nevertheless, there is no room for complacency. Thus, data collected between 1982 and 1984 showed that 28% of mothers were aged <25 and had therefore been eligible for vaccination as schoolgirls, and 60% for postpartum vaccination (E. Miller, personal communication). It must be hoped that the recent improvement in vaccination uptake aimed to increase the proportion of schoolgirls vaccinated from the current 84% to over 90%, will, in due course, reduce the incidence of maternal rubella. In the meantime, emphasis must be placed on ensuring that rubella-susceptible women of child-bearing age are offered rubella vaccination. Whilst it is encouraging that there has been an increase in the number of adult women vaccinated, in achieving this laudable objective, some women, despite adequate precautions, have been inadvertently vaccinated whilst pregnant or have become pregnant shortly afterwards. Indeed, during the last 5 years, between 19 and 33% of all rubella-associated terminations were the result of rubella immunization (OPCS 1983).

What are the risks of vaccinating rubella-susceptible women in pregnancy? Since 1971 the Center for Disease Control in Atlanta has been co-ordinating a prospective study to detect the rubella-induced fetal abnormalities following rubella vaccination within a period of 3 months before to 3 months after presumed conception (Centers for Disease Control 1984*a*). All 94 rubella-susceptible women electing to go to term, who had received either HPV-derived or Cendehill vaccines (Cendehill is one of the two licensed in the UK), were delivered of infants without any rubella-associated defects, although three infants had serological evidence of intrauterine infection. The RA27/3 vaccine, licensed in the UK in 1972, but not until 1979 in the USA, may be more potent than others, perhaps because the vaccine strain has had a less extensive passage history in culture. Despite this, it is encouraging that all of 121 infants born to 119 rubella-susceptible women, who elected to go to term, were free from rubella-induced defects and only one had serological evidence of infection; 45 of these women were vaccinated during the high-risk period of 1 week before to 4 weeks after conception. There was serological evidence to suggest that intrauterine infection had occurred in 2 of the 150 infants whose mothers' immune status was unknown when vaccinated but follow-up studies showed that both these infants developed normally.

On the basis of these studies, it has been calculated that the theoretical maximum risk of rubella-induced defects following administration of the RA27/3 vaccine is of the order of 3%; if the 95 infants exposed to the two other vaccines are included, the risk is reduced to 1·7%. Thus, the theoretical risk of malformation is no greater than for women who have not been given rubella vaccine. Similar findings, but on a somewhat smaller series of rubella-susceptible women, have recently been reported from the FRG and the UK (International Symposium on 'The Prevention of Congenital Rubella Infection' 1984). In the UK excellent co-operation between obstetricians and the Congenital Rubella Surveillance Registry has been achieved. As a result of this it is hoped to provide much useful additional data to supplement other studies. Although the results of the above studies are encouraging, since rubella vaccine strains have been recovered from products of conception of rubella-susceptible women given rubella vaccine and because vaccine strains may occasionally induce a fetal immune response, albeit rarely, it would seem prudent to follow the suggestions of the US Immunisation Practice Advisory Committee (Centers for Disease Control 1983) which advise that:

(1) Pregnancy should remain a contraindication to rubella vaccination because of the theoretical risk, albeit small, of congenitally acquired rubella. Pregnancy should be avoided for 3 months after vaccination.

(2) Reasonable precautions should be taken to avoid vaccination of pregnant women.

(3) If a vaccinee is found to be pregnant within 3 months of conception, the risk of rubella-induced defects is so small as to be negligible. Thus, rubella vaccination of pregnant women should not ordinarily be a reason to consider termination of pregnancy as a routine measure although that decision should be made by the patient and those responsible for her clinical management.

Many of the problems discussed above would be resolved if a substantially higher proportion of persons were immunized in childhood. Unlike the situation in the UK, the rubella vaccination programme in the USA has already resulted in a marked reduction in postnatally and congenitally acquired rubella (Centers for Disease Control 1984*b*).

Pressure is periodically applied to the DHSS to bring its vaccination policy in line with that of the USA in which preschool children of both sexes are given rubella vaccine. However, in the USA rubella vaccine is given as as a combined vaccine with measles and mumps (MMR). Since children are not allowed to attend primary school without evidence of vaccination against pertussis, diphtheria, tetanus, polio, measles and rubella, it is not surprising that the incidence of these infections has declined markedly. It is extremely unlikely that such coercive measures would be acceptable in the UK. An alternative two-stage proposal has recently been introduced in Sweden (Christenson *et al.* 1983), rubella vaccine being offered to boys and girls during their second year of life and again to girls at the age of 12. Whilst the US and Swedish policies may reap reward in their respective countries, such strategies may not achieve success in the UK. Indeed, Knox (1980) and Anderson & May (1983) have used mathematical models to show why such policies may not work in the UK. Thus, the mean age for contracting rubella in the UK is about 9 (approximately 50% are seropositive at this age). If the population is vaccinated at an age above that at which rubella is usually contracted, little change in the pattern of infection in younger children will result. If, however, preschool children are vaccinated, this being before the age at which rubella is usually acquired, the mean age for acquiring rubella will shift to an older age group, which may result in more infection occurring among adolescents and in women of child-bearing age. This phenomenon can only be avoided by ensuring that extremely high vaccination uptake rates are achieved among preschool children. The current rate of acceptance of measles vaccine in the UK (about 60%) does not provide an optimistic forecast for high rubella vaccination uptake rates among preschool children should a change in policy be considered.

It must therefore be hoped that the rubella vaccine programme, recently intensified, will in due course result in a reduction in maternal rubella. In the meantime, obstetricians in the UK will continue to be confronted with problems relating to women who have been exposed to, or who have developed, rubella-like illnesses in pregnancy for some time to come. Close liaison between obstetricians and their laboratory colleagues will minimize errors in diagnosis or interpretation of results and, in many instances, will go a long way to allay patients' anxieties during investigation.

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Is group B streptococcal screening during pregnancy justified?

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Summary. Twenty-eight per cent of women investigated during pregnancy were carriers of group B streptococci (GBS). The use of broth enrichment was the most significant factor in determining GBS carriage rates. GBS carriage decreased during pregnancy. Transmission of GBS from mother to baby was related to vaginal carriage but rectal carriage in pregnancy was the best predictor of maternal carriage at term. Rectal and vaginal swabs taken at 28 and 36 weeks correctly predicted 92% of intrapartum GBS carriage. Although accurate prediction of intrapartum GBS carriage is possible, mass screening for GBS in pregnancy is unlikely to be cost-effective in those countries with a low incidence of neonatal GBS sepsis.

Group B streptococci (GBS) are now well recognized as a major cause of sepsis in the neonatal period. As the source of the organism in infants who develop the more common early-onset form of the syndrome is the maternal genital tract, many epidemiological studies of GBS carriage have centred on colonization of pregnant women. Various sampling and culture techniques have been used and the wide range of reported GBS colonization rates probably reflects differences in study design rather than true epidemiological variations.

The use of systemic antibiotics during labour to interrupt mother/baby transmission of GBS has been demonstrated by several groups (Boyer *et al.* 1982; Yow *et al.* 1979). However, the implementation of such prophylaxis into routine clinical practice would entail the introduction of a screening programme for GBS carriage during pregnancy (Easmon *et al.* 1983). Early reports suggested GBS colonization of pregnant women to be intermittent or transient making prediction of intrapartum carriage difficult. However, recent studies employing more thorough sampling techniques have suggested that carriage during pregnancy is more stable. In this paper we have examined the comparative efficiency and cost-effectiveness of different sampling procedures for the prediction of intrapartum GBS carriage—particularly in relation to the site, timing, and processing of such samples.

Patients and methods

Sampling

Informed consent was obtained from the pregnant women taking part in the project. Low vaginal and anorectal swabs were taken when possible at booking, 28 weeks, 36 weeks, and on admission in established labour. Newborns were sampled within 24 h of birth and on discharge from hospital at four sites—rectum, umbilicus, ear, and external nares. Some babies were sampled on just one occasion.

Processing

Swabs were transported to the laboratory in Amies transport medium and normally cultured within 4 h. Maternal swabs were processed in two ways. Firstly, directly onto blood agar and Islam's starch serum agar (Islam 1977) supplemented with nalidixic acid (15 mg/l) and gentamicin sulphate (4 mg/l), the plates then being incubated anaerobically overnight at 37 °C using the Gaspak system (BBL) (Easmon *et al.* 1981). Secondly, following direct plating the swabs were placed in Todd Hewitt Broth (BBL) supplemented with 5% (v/v) sheep red cells, 15 mg/l nalidixic acid, and 4 mg/l gentamicin sulphate. After overnight incubation the resulting broth culture was subcultured onto blood agar and Islam's starch serum agar (without antibiotic supplement) and the plates again were incubated overnight anaerobically at 37 °C. Colonies of most GBS are β-haemolytic on blood agar and produce a characteristic orange-yellow carotenoid pigment when incubated anaerobically on Islam's medium. Presumptive GBS were serogrouped and serotyped using a coagglutination technique.

Swabs from babies were cultured only by the broth enrichment technique.

Analysis

Maternal carriage was graded according to the number of colonies on direct plating (>50, +++; 10–50, ++; <10, +) or presence only on enrichment (E). These data together with clinical details of each pregnancy were computer-coded and analysed using the Statistical Package for the Social Sciences (SPSS).

Results

GBS colonization in pregnancy

A total of 1457 women were studied, although not all were swabbed at every sample visit. Table 1 shows the GBS isolation rates using anorectal and low vaginal swabs or a combination of the two, with either direct culture alone or direct culture plus broth enrichment. Isolation rates of GBS were significantly higher at both sites when broth enrichment was used (28% *vs* 17%; $\chi^2 = 41$, $P<0{\cdot}001$). Neither rectal nor vaginal swabs detected total GBS carriage and there was no difference between rectal and vaginal GBS carriage rates.

The more often individual women were swabbed during pregnancy the higher the GBS isolation rate, rising from 23% among those sampled once to 33% among those swabbed four times (Fig. 1). GBS carriage rates appeared to decline steadily as pregnancy proceeded (Table 2). Intrapartum GBS carriage was significantly lower than that at booking ($\chi^2 = 8{\cdot}7$, $P<0{\cdot}01$), but not compared with that at 28 or 36 weeks gestation. Of 131 GBS carriers swabbed three times during pregnancy, 55 (42%) were positive on each occasion.

Table 1. Group B streptococcal (GBS) carriage in 1457 pregnant women

	GBS carriage (*n* = 1457)	
Sample site	Direct plating only *n* (%)	Direct plating with enrichment *n* (%)
Rectal and low vaginal	249 (17·1)	414 (28·4)
Rectal	185 (12·7)	342 (23·5)
Low vaginal	214 (14·7)	360 (24·7)

Transmission of GBS from mother to baby

Of the 414 women who carried GBS at some time during pregnancy, 337 gave birth to babies who were investigated for GBS carriage, and of these 87 (26%) were found to be colonized with the organism. None of the infants in the study population developed clinical infection. When only intrapartum carriage was considered, 52 (35%) of the babies born to 148 colonized mothers were found to carry GBS. In 141 of this latter group we analysed the effect of intrapartum events on the transmission of GBS from mother to baby (Table 3; data were missing in

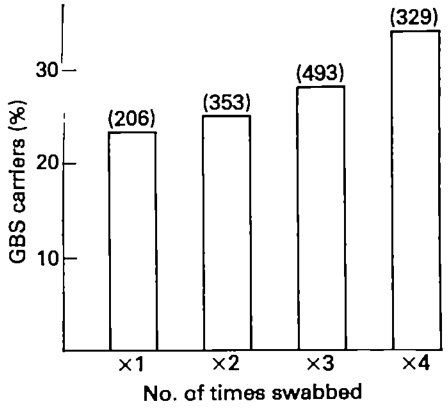

Fig. 1. Group B streptococcal carriage in pregnancy. Effect of repeated sampling on carriage rates.

Table 2. Group B streptococcal (GBS) carriage in pregnant women during pregnancy and intrapartum

Sampling time	No. of women sampled	GBS carriers *n* (%)
Booking	818	192 (23·5)
28 weeks	1116	231 (20·7)
36 weeks	895	177 (19·8)
Intrapartum	887	151 (17·0)

Table 3. Effect of intrapartum events on transmission of group B streptococci from mother to baby in 141 carriers

	Non-transmittors ($n = 102$) *n* (%)	Transmittors ($n = 39$) *n* (%)
Any operative delivery	26 (25)	6 (21)
Caesarean section	9 (9)	2 (5)
Labour >10 h	33 (32)	18 (46)
Ruptured membranes >10 h	20 (20)	12 (31)
Intrauterine monitor*	69 (70)	28 (72)
Antibiotics	24 (25)	0 (0)†

*Fetal scalp electrode or uterine pressure monitor.
†Significance of difference between the two groups $P<0{\cdot}001$.

the other seven patients). Although neither vaginal operative delivery, prolonged labour or prolonged rupture of membranes (≥10 h) had a statistically significant effect on GBS transmission, these factors were associated with increased transmission rates of GBS from mother to baby. As reported previously (Easmon *et al.* 1983), the use of antibiotics during labour eliminated mother-to-baby transmission of the organism.

Fig. 2 shows the effect of the heaviness of intrapartum rectal and vaginal GBS colonization on mother-to-baby GBS transmission. The heaviness of vaginal, but not of rectal GBS carriage, was directly related to the transmission rate.

Prediction of intrapartum GBS carriage

A combination of anorectal and low vaginal sampling at both 28 and 36 weeks correctly predicted 132 (92%) of 144 intrapartum GBS carriers (Table 4). Inclusion of swabs taken at booking did not significantly improve this percentage (92% *vs* 94%, $\chi^2 = 0{\cdot}63$, $P>0{\cdot}5$) and resulted in a marked increase in the number of false-positive results, (women with positive antenatal GBS results but negative intrapartum results) (36% *vs* 17%, $\chi^2 = 36$, $P<0{\cdot}001$). When screening at 36 weeks alone was considered there was a fall in the rate of correct prediction of intrapartum GBS carriers, but this was not significant (92% *vs* 84%, $\chi^2 = 3{\cdot}3$, $P>0{\cdot}05$) and was parallelled by a reduction in the number of false-positive results (17% *vs* 8%, $\chi^2 = 20{\cdot}6$, $P<0{\cdot}001$). Measured in relation to intrapartum GBS carriage, the majority of which was at term (37 weeks gestation or more), screening at 28 weeks alone was less effective than at 36 weeks alone ($\chi^2 = 5{\cdot}2$, $P<0{\cdot}05$).

Taking 36 weeks sampling, Tables 5 and 6 show the greater value of the rectal swab as against the vaginal swab as a predictor of intrapartum GBS carriage and the importance of using enrichment broth culture.

Discussion

Comparisons of GBS colonization rates in different population groups are made difficult by variations in study design. A survey of published research shows that those studies employing a GBS enrichment procedure, repeated swabbing during pregnancy, or the sampling of multiple sites, report GBS carriage rates of over 20% in pregnant women (Anthony *et al.* 1978, 1981; Badri *et al.* 1977; Dillon *et al.* 1982; Hoogkamp-

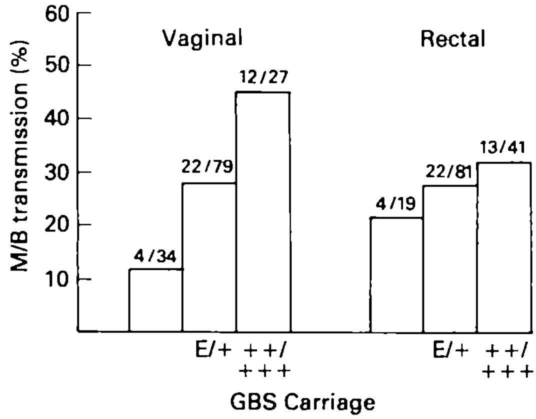

Fig. 2. Effect of heaviness of rectal and vaginal intrapartum group B streptococcal carriage on mother/baby transmission. E, culture on enrichment only.

Table 4. Predictive value of GBS screening during pregnancy using anorectal/vaginal swabs with enrichment

	Intrapartum GBS positive (n = 151)		Intrapartum GBS negative (n = 736)	
Screen time (weeks)	No screened*	Screen negative† n (%)	No. screened	Screen negative n (%)
Booking/28/36	136	8 (6)	303	193 (64)
28/36	144	12 (8)	488	403 (83)
36	108	17 (16)	545	501 (92)
28	128	36 (28)	630	563 (89)

*Antenatal sampling data was not complete for all those mothers screened for intrapartum GBS carriage
†Screen negative = negative for GBS at *every* defined antenatal sampling time.

Table 5. Comparison of swab site at 36 weeks for prediction of intrapartum GBS carriage

	Intrapartum GBS carriers (n = 151)	
Swab site	No. screened	Screen negative n (%)
Low vaginal	108	36 (33)
Rectal	107	24 (22)
Rectal and low vaginal	108	17 (16)

Table 6. Effect of broth enrichment on predictive value of 36 week swabs for intrapartum GBS carriage

	Intrapartum GBS carriers (n = 151)	
Culture of swabs	No. screened	Screen negative n (%)
With enrichment	108	17 (16)
Without enrichment	108	49 (45)

Korstanje *et al.* 1982). The most significant factor is the use of the broth enrichment method. Unlike Badri *et al.* (1977) and Dillon *et al.* (1982), we found no difference between rectal and vaginal GBS carriage rates. The explanation may be our use of low vaginal swabs. Anthony *et al.* (1978) using this site, which approximates more to a perineal sample, had similar results to our own.

Intermittent GBS carriage during pregnancy was reported by Anthony *et al.* (1978) and Ferrieri *et al.* (1977). However, both studies only used vaginal swabs. Two more recent studies with multiple site sampling have shown more consistent patterns of colonization (Dillon *et al.* 1982; Hoogkamp-Korstanje *et al.* 1982). Our own results support Dillon's concept of the rectal site as the major deteriminant of GBS carriage.

Previous estimates of mother-to-baby transmission rates range from 40 to 70% (Aber *et al.* 1976; Ferrieri *et al.* 1977; Anthony *et al.* 1978; Yow *et al.* 1979; Ancona *et al.* 1980). Our own rather lower figure of 35% can be explained by differences in study design. We did not investigate babies for GBS immediately after birth on the grounds that we wished to assess true colonization, not merely coating with GBS. We also defined maternal carriage in terms of both rectal and vaginal carriage.

Although rectal colonization is the major determinant of GBS carriage during pregnancy, it is vaginal carriage, and more particularly the heaviness of vaginal carriage, that determines the rate of GBS transmission from mother to baby. Those features of labour that increased the length of exposure of the baby to maternal bacteria (prolonged labour and premature rupture of membranes) increased the likelihood of infant colonization. They are also associated with an increased risk of neonatal GBS sepsis (Anthony & Okada 1977). In contrast we found no relationship between GBS transmission and operative vaginal delivery, the insertion of intrauterine monitors, or the number of vaginal examinations.

Systemic intrapartum antibiotic prophylaxis is effective in preventing the transmission of GBS to the newborn (Easmon *et al.* 1983). To be selective, however, a reliable means of predicting GBS carriage in labour must be used. Ferrieri *et al.* (1977) found GBS carriage in the third trimester to be a poor predictor of intrapartum carriage but used vaginal swabs only without broth enrichment. Sampling at both 28 and 36 weeks and using vaginal and rectal swabs and broth enrichment it was possible to identify 92% of those parturients who subsequently were colonized with GBS during labour. The addition of a third set of samples taken at booking did not significantly improve this figure, merely increasing the number of predicted carriers who were intrapartum culture negative. Analysed alone, 36-week swabs were almost as good a predictor of intrapartum carriage as 28- and 36-week swabs combined. However, sampling at 36 weeks alone would effectively miss the preterm neonatal group in whom GBS sepsis is most dangerous.

Accurate prediction of intrapartum GBS carriage is possible. In the UK an overall rate of 0·3 GBS infections per thousand live births (Mayon-White 1982) would mean screening over 3000 women to detect one case of GBS sepsis. With materials and labour this would cost at least £3–4000. Such expenditure would not, of course, prevent late onset GBS sepsis or early onset nosocomial GBS disease. In certain centres in the USA with GBS infection rates over 10 times those in the UK and Europe the balance of cost-effectiveness of mass screening for GBS in pregnancy may be very different.

The knowledge that accurate prediction is possible may be applied usefully to more selective screening even where mass screening is not indicated. For this approach suitable maternal immunological and obstetric risk factors for neonatal GBS sepsis must be established.

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Prophylaxis of thromboembolism in pregnancy: an alternative

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Summary. Twenty-six pregnancies in women who had one or more episodes of thromboembolism in the past were managed by a regimen in which routine antenatal prophylactic anticoagulation was not given, apart from during delivery which was covered with intravenous infusion of dextran 70. After delivery, these patients received either subcutaneous heparin for 6 weeks or subcutaneous heparin for 1 week, followed by 5 weeks of warfarin. One patient (4%) possibly developed an episode of thromboembolism in the antenatal period. There were no episodes of postnatal thromboembolism. There were two spontaneous mid-trimester abortions and no perinatal losses. There were no significant complications or reactions related to the use of dextran, heparin or warfarin.

In England and Wales, pulmonary embolism is the leading cause of maternal death (DHSS 1982). For those with a previous episode of thromboembolism, the risk of recurrence has been estimated as 12% (Badaracco & Vessey 1974).

Antenatal prophylaxis with warfarin or heparin is widely used to reduce the risk of recurrent thromboembolism in pregnancy (de Swiet *et al.* 1980). Warfarin has fallen out of favour because of the reported fetal complications such as chondrodysplasia punctata (Becker *et al.* 1975; Abbott *et al.* 1977), optic atrophy, microcephaly and mental retardation (Holzgreve *et al.* 1976) as well as retroplacental and intracerebral bleeding (Villasanta 1965). Maternal bleeding has also been noted (de Swiet *et al.* 1977). Subcutaneous heparin prophylaxis was shown to be effective both in gynaecological surgery (Ballard *et al.* 1973) and in pregnancy (Bonnar 1976). As heparin does not cross the placenta, this treatment has been regarded as safe for the fetus as well as for the mother and in a controlled trial (Howell *et al.* 1983), the occurrence of complications with a low-dose regimen was similar to that in an untreated group. Nevertheless, complications such as an increased risk of abortion, prematurity and stillbirth (Hall *et al.* 1980) and thrombocytopenia (Cines *et al.* 1980; Chong *et al.* 1982) have been reported. In addition, the recent finding of a dose-related effect of bone demineralization as assessed radiologically in all the women who were given low-dose heparin for more than 20 weeks during pregnancy (de Swiet *et al.* 1983) supports earlier observations of osteopenia associated with heparin therapy (Griffith *et al.* 1965; Avioli 1975; Wise & Hall 1980). This effect was still present in women studied up to 24 months after the cessation of therapy. Furthermore, both deep vein thrombosis and pulmonary embolism are three times more frequent in the puerperium than in the antenatal period (Aaro & Juergens 1971). For these reasons, we have changed our policy and have abandoned antenatal prophylaxis whilst retaining intrapartum and postpartum prophylaxis. We have also used dextran rather than subcutaneous heparin in labour to permit the use of epidural anaesthesia (Crawford 1978). In this report, we present our experience with this management scheme.

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Patients and methods

All patients with a previous history of thromboembolism were referred to the Obstetric Medicine Clinic, where we tried to manage them in a uniform manner. Information was obtained from the hospitals where they were originally treated. The patients were only managed under the following scheme if the diagnosis at the time of the original episode was established by venography or lung scan, or if they had been treated with anticoagulants for at least 6 weeks. Six of the patients (23%) had their original episode of thromboembolism in association with pregnancy (Table 1). The risks of recurrence and of heparin prophylaxis were explained. Patients were asked to report immediately should they have chest symptoms or features of deep vein thrombosis.

Two patients received anticoagulants before labour; one possibly developed a pulmonary embolus and was treated (see below). The other patient, whose previous deep vein thrombosis occurred at 38 weeks gestation, was given subcutaneous heparin from 37 weeks of pregnancy until labour when she received dextran. She was managed in this way according to the wishes of the referring obstetrician.

During labour or before caesarean section, an intravenous infusion of 500–1000 ml of dextran 70 (Macrodex, Pharmacia) was given over a period of 8–12 h. Blood was saved for cross-matching before starting the infusion. Where general anaesthesia was given, the dextran infusion was started before the procedure.

After delivery, prophylactic anticoagulation was offered to all the patients, starting with 8000 units of heparin subcutaneously twice daily for the first week in the hospital and then continued by self-administration for another 5 weeks at home as described by Howell *et al.* (1983). Alternatively, oral warfarin was offered after the first week to patients who disliked self-injection at home. Patients were free to choose between the two therapies. Heparin levels were not routinely assayed. Patients taking warfarin were monitored by weekly tests to maintain the prothrombin ratio between 2·0 and 3·0. The patients were seen again at the medical clinic 3 and 6 weeks after delivery. Treatment was stopped 6 weeks postpartum.

Results

We studied 26 pregnancies in 24 patients, 10 of whom were primigravidae. Their mean age was 31·1 (SD 5·3) years. Only one patient (4%) had an episode of possible thromboembolism. She was admitted to another hospital at 23 weeks gestation with chest pain, given intravenous heparin for 5 days, which was stopped when a lung scan showed no abnormality. As she had a medical history of previous confirmed pulmonary embolus, she was treated with intrapartum dextran and postpartum heparin, according to the above regimen.

None of the patients developed thromboembolism after delivery. Table 1 indicates the sites of occurrence and associated features of previous thromboembolic episodes. The outcome of pregnancy and its complications are shown in Table 2. There were no perinatal losses. There were two mid-trimester abortions (at 18 and 20 weeks) occurring in consecutive pregnancies in the same patient who also suffered from recurrent pyelonephritis and chronic hypertension Of the remaining 24 pregnancies, three (12%) were delivered by caesarean section (Table 3). Of the two preterm deliveries, one was in a patient with severe pre-eclampsia necessitating delivery at 33 weeks. The other delivery

Table 1. Previous history of thromboembolism (no of pregnancies = 26)

Site of previous thromboembolism	No of episodes	Associated factors			
		Oral contraception	Pregnancy	Other	None
Deep vein thrombosis	16 (62%)	7	5	1*	3
Deep vein thrombosis plus pulmonary embolism	4 (15%)	2			2
Pulmonary embolism	6 (23%)	4	1		1
Total	26 (100%)	13 (50%)	6 (23%)	1 (4%)	6 (23%)

*Following leg fracture.

Table 2. Pregnancy complications and outcome (no of pregnancies = 26)[*]

Pregnancy complications		
Threatened abortion	3	
Antepartum haemorrhage	0	
Antenatal pulmonary embolism	1	
Chronic hypertension	2	(in the same patient)
Recurrent pyelonephritis	2	
Pre-eclampsia	4	
Primary postpartum haemorrhage	2	
Secondary postpartum haemorrhage	1	
Pregnancy outcome		
Midtrimester abortion		(in the same patient)
Delivery before 37 weeks	2	
Perinatal death	0	
Admission to special care baby unit	1	
Congenital malformation (undescended testis)	1	
Mean birthweight (g) (excluding abortions)	3307	(SD 647)

[*] Two patients were each treated in two pregnancies. One of these patients had both her pregnancies complicated by hypertension, pyelonephritis and midtrimester abortion

occurred at 36 weeks in the patient who had been treated with heparin for thromboembolism (see above). The mode of delivery and anaesthesia used are shown in Table 3, together with the use of anticoagulants. All patients received an intrapartum dextran infusion. In the puerperium, two patients refused heparin, while another two received different doses of heparin (5000 units and 10 000 units twice daily respectively) due to a prescribing error. Similar numbers received heparin alone (13) or warfarin (11). Two patients had primary postpartum haemorrhage not requiring blood transfusion. The only side-effect seen was minor bruising at the injection site in several patients. Bleeding did not occur in any of the patients taking warfarin.

Discussion

In this series, recurrence of thromboembolism in the antenatal period occurred in no more than one in 26 pregnancies (4%). It is possible that some episodes of subclinical deep vein thrombosis or pulmonary embolism remained undiagnosed since, in postoperative studies, only 25% of those with scan-positive pulmonary embolism had clinical signs (Browse *et al.* 1976) and only 31% of isotopically confirmed deep vein thromboses were clinically apparent (Kline *et al.* 1975). However, no such studies have been performed in healthy pregnant women and the likelihood of major occult thrombosis in these patients is small. The previous estimate of 12% recurrence risk in pregnancy in patients who have thromboembolism in the past was based on a postal survey (Badaracco & Vessey 1974). Furthermore, any patient who has had thromboembolism before and develops suggestive symptoms or signs is likely to be readily diagnosed as having a recurrence without the necessary objective tests being performed. The recurrence risk may therefore be less than 12% in pregnancy in general, and even lower in the antenatal period as the greater part of these episodes occur postpartum (Aaro & Juergens 1971). For these reasons we believe that the place of routine antenatal prophylactic anticoagulation should be reconsidered in this group of patients.

The combination of intrapartum dextran and postpartum anticoagulation seemed to be both safe and effective in the prevention of clinical episodes of thromboembolism. Wallach (1972) showed that intravenous dextran was effective in the treatment of pregnancy associated throm-

Table 3. Details of delivery and prophylaxis

			Postpartum prophylaxis		
Mode of delivery	Epidural anaesthesia	General anaesthesia	Heparin only	Heparin and warfarin	None
Spontaneous vaginal delivery (15)	4		8	5	2
Forceps delivery (6)	6		2	4	
Caesarean section (3)	3		1	2	
Abortions (2)	1	1	2		
Total	14 (54%)	1 (4%)	13 (50%)	11 (42%)	2 (8%)

bophlebitis. Pre- and post-operative infusion of dextran in general surgical cases (including pelvic surgery) has also been successful in reducing the incidence of postoperative pulmonary embolism (Kline *et al.* 1975; Browse *et al* 1976, Bonnar & Walsh 1972) and the effect was comparable to subcutaneous heparin therapy (Gruber *et al* 1977, 1980). The anti-thrombolic action of dextran is not fully understood. Several mechanisms such as reduction of inhibition of fibrinolysis (Carlin & Saldeen 1978), coating of vascular endothelium and platelets and reduced activation of clotting factors have been suggested Perhaps more important in labour and caesarean section is the decrease in blood viscosity and improvement in blood flow in the legs during and after infusion (Dormandy 1971). When given before delivery, dextran may counter the initiation of thrombosis related to stasis in the pelvic and leg veins, especially if epidural anaesthesia is given

The use of dextran in contrast to heparin (Crawford 1978) permits epidural anaesthesia This could be a factor influencing perinatal morbidity (Howell *et al.* 1983) since in many units the management of complicated labour is very dependent on epidural anaesthesia. In addition, deep vein thrombosis has been shown to be significantly reduced with spinal subarachnoid block as compared with general anaesthesia in patients undergoing total hip replacement (Thorburn *et al* 1980). Thus dextran and epidural anaesthesia may potentiate each other in preventing thromboembolism.

Dextran is not without risk, as hypersensitivity reactions have been reported (Michelson 1968; Fothergill & Heaney 1976), some of which have been fatal (Fanous *et al.* 1977; Wilson & Brown 1978). In these two fatal cases the rates of infusion were rapid, i.e. 50 ml in 2 min and 200 ml in 10 min. Ring & Messmer (1977) found that the incidence of anaphylactoid reactions with dextran was 0·032%. We have not observed any hypersensitivity reactions. Our infusion rate was slow allowing adverse reactions to be recognized before the infusion of a large volume of dextran.

Smith (1973) found that abdominal and pelvic haematomas were common in patients who received dextran 70 after major gynaecological operations. However, we encountered no bleeding problems or wound haematoma. Gruber *et al.* (1980) also found that dextran was safer than heparin and the need for withdrawal of therapy was less common.

Anticoagulants were given for 6 weeks in the postnatal period as pulmonary embolism can occur several weeks after delivery. The use of warfarin is possible in mothers who breast feed their babies, as warfarin does not enter breast milk in significant quantities (Orme *et al.* 1977) It can therefore be offered as an alternative to heparin.

Although we have only studied a relatively small number of patients, our management appears to be effective and without serious complications. We therefore suggest that for patients with a history of a single episode of thromboembolism, conventional antenatal prophylaxis with heparin is not necessary, while intrapartum dextran infusion and postpartum anticoagulation are both safe and probably effective in preventing thromboembolism. However, antenatal prophylaxis remains necessary in some special circumstances, such as in patients with antithrombin III deficiency, and may be necessary in others such as those who have had multiple previous episodes of thromboembolism. Further larger studies using our regimen are required to investigate its efficacy and possible side-effects more clearly. Alternatively, short, lower-dose regimes of heparin may also be effective in the antenatal period, and may lack the side-effects of conventional prophylaxis. However, such management would also require rigorous clinical evaluation.

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Dramatic increase of placental protein 5 levels following injection of small doses of heparin

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Summary. In the course of an investigation on the effects of thyroid releasing hormone in pregnant women we noted a dramatic increase in the levels of placental protein 5 (PP5) in maternal blood. This increase ranged from 10 times to over 40 times the basal levels. Further study showed that the rise was associated with the use of heparin to maintain the patency of the cannula through which the samples were collected. Furthermore, the phenomenon appeared to be systemic rather than local, and may well be due to a direct effect of heparin on PP5 secretion by the placenta.

Placental protein 5 (PP5) is one of a group of 'specific' proteins of the human placenta (Bohn 1970). It has the electrophoretic mobility of a β-1-globulin, a molecular weight of 36 000 daltons and a carbohydrate content of 20% (Bohn 1972; Bohn & Winckler 1977). PP5 is produced by the syncytiotrophoblast (Sedlacek *et al.* 1976; Seppala *et al.* 1979; Bohn 1976) and becomes detectable in maternal serum around 6–10 weeks gestation (Obiekwe *et al.* 1979; Salem *et al.* 1980). Recent studies have suggested that PP5 is related to the blood coagulation system during pregnancy· in particular that it may have a biological role analogous to antithrombin III (Salem *et al.* 1981*a*). The levels of PP5 are elevated in obstetric conditions associated with coagulation disturbances, such as placental abruption (Salem *et al.* 1981*b*), pre-eclampsia and eclampsia (Salem *et al.* 1983; Lee *et al*, 1981).

In the course of an entirely separate study on the endocrinological effects of thyroid releasing hormone (TRH) in mid-pregnancy, we noted that the experiment was associated with a dramatic increase in maternal PP5 levels. We now report this phenomenon in detail.

Subjects and methods

Sixteen women at 12 to 20 weeks gestation who were scheduled to undergo therapeutic abortion gave informed consent to participate in this investigation.

TRH study

The 16 women included in the study had a butterfly cannula inserted into a forearm vein and blood samples were obtained 30 to 15 min before the injection of 200 μg of TRH, and thereafter at intervals of 10 min for 40 min, and then at 60, 90 and 120 min. After each sample was withdrawn the cannula was flushed with 200 μl of normal saline containing approximately 200 i.u. of heparin (Weddell Pharmaceuticals Ltd, London). The blood samples were left to clot and serum was stored at −20°C.

Heparin study

Three women were investigated. One woman followed the protocol of the TRH study but in addition had blood samples taken simultaneously from the antecubital vein of the opposite arm. Serum samples were stored at −20°C. The second subject received an intravenous injection of 500 i.u. of heparin; blood samples were taken via a butterfly cannula at 1-min intervals for 10 min, and the serum was stored at −20°C. The third subject had an intravenous injection of 500 i.u. of heparin, a blood sample was taken 5 min before the heparin injection and another sample 5 min afterwards. The samples were dispensed as 2-ml aliquots into tubes containing 0, 3, 6, 12, 25, 50 and 100 i.u. of heparin. The plasma was stored at −20°C.

All samples were assayed for PP5, human chorionic gonadotrophin (hCG) and human placental lactogen (hPL) using radioimmunoassays as described previously (Obiekwe *et al.* 1979; Lenton *et al.* 1981; Niven *et al.* 1972)

Results

TRH study

There was a dramatic rise in PP5 levels during the course of the experiment (Fig. 1*a* and *b*) and in all the women the levels began to rise before the injection of TRH. The maximum levels ranged from 10 to 46 times those of the basal levels and were reached at a variable time between 10 and 40 min.

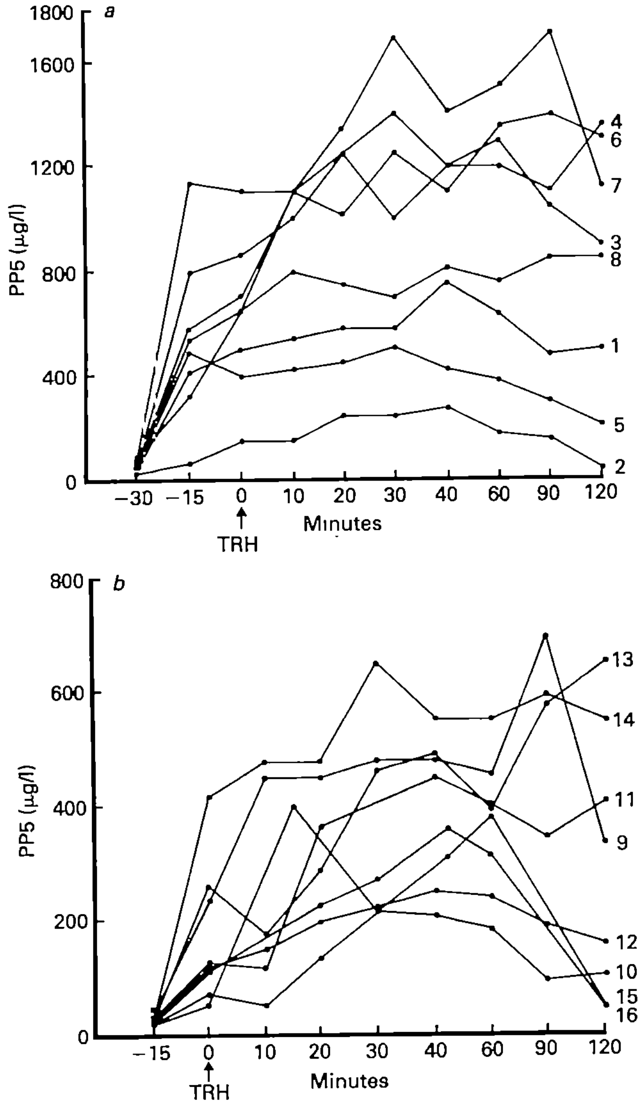

Fig. 1. PP5 concentrations in serial blood samples taken before and after an intravenous injection of thyroid releasing hormone (TRH) in 16 subjects.

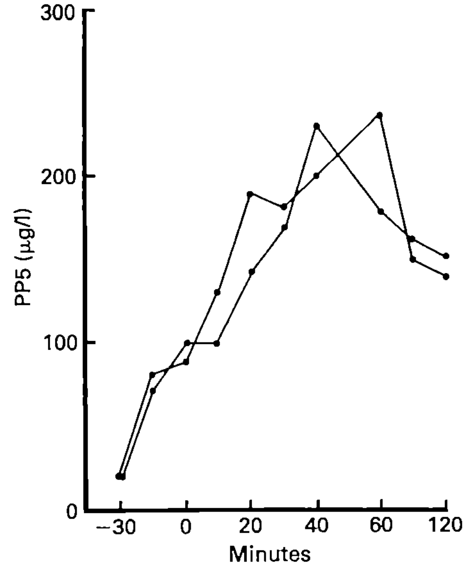

Fig. 2. PP5 concentrations in serial blood samples from the antelateral and contralateral arms in one subject before and after injection of thyroid releasing hormone (TRH)

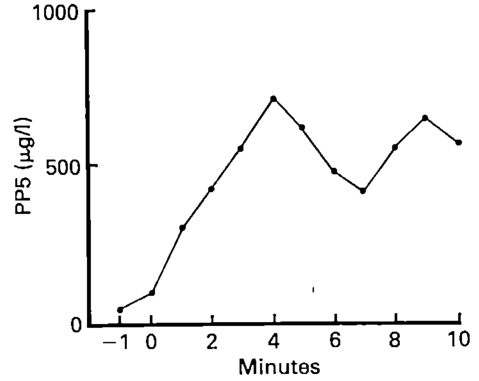

Fig. 3. The increase of PP5 levels in serial blood samples following a single intravenous injection of heparin in one subject

Heparin study

In the first woman PP5 levels in both arms showed an identical pattern, and reached a maximum after 20–60 min (Fig. 2). In the second subject, who received 500 i.u of heparin, the maximum increase in PP5 levels was found within 3 to 5 min (Fig. 3) and results in the third subject showed that the addition of heparin to blood samples produced only a small and inconsistent effect (Table 1).

hCG and hPL

There was no significant change in the levels of these proteins during any of the experiments.

Discussion

The findings described here were largely serendipitous: in the initial study levels of PP5 were measured only as part of a general group of maternal and placental products. Furthermore, it soon became apparent that the phenomenon bore no relation to TRH itself, but rather was independently associated with the procedure of intravenous cannulation and sampling. Other placental products showed no change.

Although the dramatic effect of heparin on PP5 *in vivo* has not been previously observed there is extensive evidence *in vitro* for a complex interaction between PP5 and heparin (Obiekwe *et al.* 1979). There was nothing to suggest that the massive rise observed *in vivo* was an artefact of the assay because the main effect of heparin on the assay of PP5 is to *decrease* the apparent levels of the protein. In addition, the observation in the one subject of elevated levels also in the contralateral arm (Fig. 2) clearly showed that the phenomenon was systemic and not merely localized to the site of the indwelling cannula.

Table 1. Effect of different amounts of added heparin on PP5 concentrations in blood samples obtained 5 min before and 5 min after an injection of 500 i u of heparin

	PP5 (μg/l) in samples with added amounts of heparin (i u)						
	0	3	6	12	25	50	100
Samples collected before injection of heparin	17	36	30	30	25	36	30
Samples collected after injection of heparin	440	410	470	410	360	320	320

The mechanism of the heparin effect is uncertain. The doses examined were all well below those used for therapeutic purposes and would not be expected to have a significant effect on overall coagulation status. Equally, quite small doses of heparin have been shown to stimulate release of platelet factor IV (Dawes *et al.* 1978) and fatty acids (Hovel 1982), so that potent biological effects are not unfamiliar with this polyanion. The site of the effect is also unknown: it could be on the placenta itself leading to an abrupt release of PP5; or it could be an effect of heparin on a substrate (presumably of placental origin) which is already present in the circulation. The fact that the phenomenon takes some minutes to develop (Fig. 3) would perhaps favour release from the placenta rather than an immediate action on a circulating precursor, but this argument is by no means final.

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Serum chorionic gonadotrophin (hCG), schwangerschaftsprotein 1(SP1), progesterone and oestradiol levels in patients with nausea and vomiting in early pregnancy

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Summary. Serum concentrations of human chorionic gonadotrophin (hCG), schwangerschaftsprotein 1(SP1), progesterone and oestradiol were measured in 116 pregnant women experiencing varying degrees of nausea and vomiting or no nausea at all at between 9 and 16 weeks gestation. The patients were categorized into four groups, namely asymptomatic, nausea alone, nausea and vomiting and hyperemesis gravidarum. The distribution of levels for each group were examined in relation to the calculated normal ranges. Statistically higher hCG levels were found in out-patients with nausea alone or nausea and vomiting than in the asymptomatic women. No significant differences were found between the groups for any of the other measured variables, including the progesterone/oestradiol concentration ratio.

Approximately one in two women will experience some nausea and vomiting in the early stages of pregnancy, commonly in the form of 'morning sickness' (Fairweather 1968). In a small proportion when the vomiting becomes more serious and persistent the term 'hyperemesis gravidarum' is applied.

The aetiology of nausea and vomiting in pregnancy still remains obscure but endocrine, allergic and psychosomatic factors have all been suggested as responsible. This study was designed to consider four possible endocrine factors, two placental proteins, human chorionic gonadotrophin (hCG) and schwangerschaftsprotein 1 (SP1), and two steroid hormones, progesterone and oestradiol, although SP1 and hCG might also be considered as possible allergens.

Since its discovery hCG has been considered a likely candidate for causing nausea and vomiting in pregnancy because of the early and rapid rise in placental output, and Schoeneck (1942) found higher concentrations of hCG in the urine of pregnant women who suffered from nausea and vomiting than in those who were asymptomatic. In a clinical study of patients with hyperemesis gravidarum Fairweather (1968) reported that the first trimester peak of hCG in urine and blood coincided with the most common gestation at admission, although Fairweather & Loraine (1962) had found that hCG excretion was significantly lower in patients with hyperemesis than in normal pregnant women. More recently, Soules *et al.* (1980) found no relation between absolute levels of hCG or 17-hydroxyprogesterone and the incidence or severity of nausea and vomiting in women with either normal or molar pregnancies.

Maternal blood levels of SP1 have been shown to rise throughout pregnancy (Klopper 1979), but they have not been related to nausea and vomiting in early pregnancy.

It has been suggested that nausea and vomiting are caused by progesterone deficiency, but progesterone therapy has not been shown conclusively to relieve these symptoms (Fairweather 1968) Indeed in a recent study which showed that pregnancy appeared to have a profound inhibitory effect on plasma motilin, which might be responsible for gastrointestinal hypomotility and hence the nausea, it was suggested that progesterone was the inhibiting factor (Christofides *et al.* 1982). As women taking high-dose oestrogen pills for postcoital contraception report a high incidence of nausea and vomiting, oestrogens have also been considered as a possible cause of nausea in pregnancy.

Subjects and methods

The study comprised 116 women at between 9 and 16 weeks gestation who volunteered to give a blood sample and complete a questionnaire about any nausea and vomiting experienced during the previous 7 days. With the exception of three women who were admitted to the Princess Anne Hospital with hyperemesis gravidarum, all were recruited at antenatal clinics and were otherwise unselected On the basis of information obtained from the questionnaires the women were divided into four groups as detailed in Table 1.

Table 1. Categorization of subjects with varying degrees of nausea and vomiting in the study

Group	Symptoms
1	Asymptomatic/minimal discomfort (nausea less than twice a week)
2	Nausea alone
3	Nausea and vomiting
4	Nausea and vomiting, required hospitalization

Blood samples

A single 5-ml sample of venous blood was taken from each woman at the time of interview, allowed to clot, centrifuged at room temperature and the serum dispensed into aliquots for storage at −20°. Between 10 and 18 samples were obtained for each week of gestation.

Assay

hCG was measured by a radioimmunoassay previously used for detecting threatened abortion in the first trimester of pregnancy (Masson *et al.* 1983) and based on the assay of Edmonds *et al.* (1982) Antiserum raised against the β subunit of hCG was used in the assay (SB6, National Institute of Child Health and Human Development, Bethesda) and standards were prepared from the first International Reference Preparation for hCG (1 mg/l hCG=9300 iu/l). The tracer was iodinated whole hCG (CR—121, also from National Institute of Child Health and Human Development, Bethesda)

SP1 was measured by a sensitive radioimmunoassay described by Anthony *et al.* (1980).

Oestradiol was measured with a direct ^{125}I-oestradiol radioimmunoassay kit (Code ER-155) from Steranti Research Ltd, England.

Samples were assayed for progesterone by using the in-house radioimmunoassay of the Chemical Pathology Department, Southampton General Hospital. Samples were extracted with *n*-hexane before assay, solvent-evaporated and the residues reconstituted in assay buffer. The antiserum used was obtained from Guildhay, Guildford (HPS 604/1A) and had been raised against the 11α-hydroxyprogesterone-11α-hemisuccinate-bovine serum albumin conjugate and the tracer was the 3-carboxymethyl oxime histamine conjugate of progesterone labelled with ^{125}I. Separation of bound and free antigen was by a standard polyethylene glycol/gamma globulin precipitation. The cross-reaction with pregnenolone in the assay was 0·8% but <0·01% for 17-hydroxyprogesterone.

The interassay coefficients of variation obtained with midrange samples were 8·0, 10·3, 7·4 and 6·3% for hCG, SP1, progesterone and oestradiol respectively.

Statistical analysis

All four radioimmunoassays yielded results that were positively skewed at each week of gestation and therefore a logarithmic transformation of the data was performed to obtain normally distributed data (the skewness of the data might be inherent in the use of radioimmunoassays). The geometric means are plotted in Fig. 1. Geometric means for SP1 and oestradiol were found to correspond to the 50th centiles, while the 50th centiles for hCG and progesterone were approximately 0·2 mg/l and 0·4 mg/l above their geometric means respectively. The numbers of patients within each study group distributed about the 50th centile were then calculated. A χ^2 analysis of the data was performed.

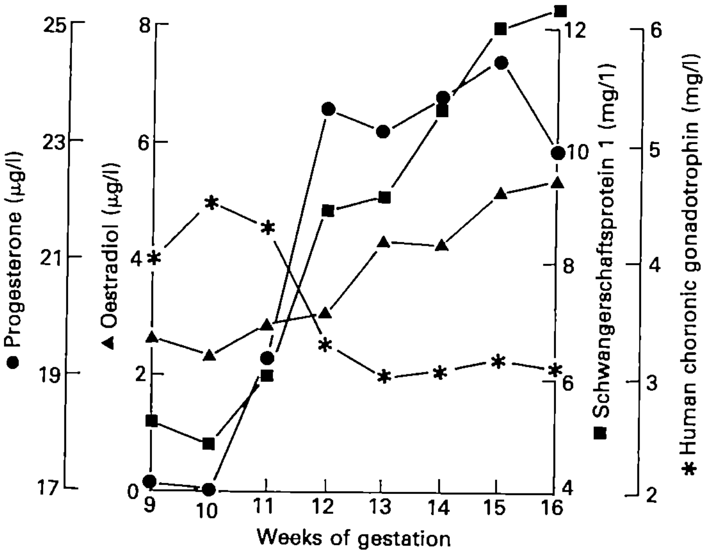

Fig. 1. Calculated geometric means for hCG, SP1, progesterone and oestradiol levels between 9 and 16 weeks gestation.

Results

Of the 113 patients who were not hospitalized 48 were allotted to group 1 (asymptomatic), 37 to group 2 (nausea alone) and 28 to group 3 (nausea and vomiting). All three groups were evenly distributed within the period of 9–16 weeks gestation.

As the results for groups 2 and 3 did not differ significantly they were combined for further analysis.

The distribution of results around the 'smoothed' 50th centiles for all four substances measured is shown in Table 2

Significantly lower hCG levels were found in the asymptomatic women than in those with nausea and vomiting, ($P<0\cdot05$) but the levels of SP1, progesterone and oestradiol were similar in the two groups.

Table 3 shows the distribution of hCG results at each week of gestation. Eleven of the 28 women in group 3 were taking anti-emetics (Maxolon, Avomine and Debendox). There were no significant differences in the SP1 and hCG levels between those who took anti-emetics and those who did not.

Of the three patients with nausea and vomit-

Table 2. Distribution of values for hCG, SP1, progesterone and oestrogen around the 50th centile in women with or without nausea and vomiting

	Asymptomatic (n=48)	Nausea and vomiting (n=65)	Total (n=113)	Significance
hCG				
<50th centile	30	26	56	$\chi^2=4\cdot72$
>50th centile	18	39	57	$P<0\cdot05$
SP1				
<50th centile	28	31	59	$\chi^2=0\cdot86$
>50th centile	20	34	54	NS
Progesterone				
<50th centile	23	33	56	$\chi^2=0\cdot56$
>50th centile	25	32	57	NS
Oestradiol				
<50th centile	26	31	57	$\chi^2=0\cdot24$
>50th centile	22	34	56	NS

Table 3. Distribution of hCG results about the 50th centile at each week of gestation

Week of gestation	No of patients	Asymptomatic		Nausea & Vomiting	
		<50	>50	<50	>50
9	10	3	1	2	4
10	17	4	3	4	6
11	13	2	3	5	3
12	18	4	2	4	8
13	18	6	4	4	4
14	14	3	1	4	6
15	13	5	2	1	5
16	10	3	2	2	3
Total	113	30	18	26	39

ing who required hospitalization (group 4) two showed levels above the corresponding 50th centile values for hCG, progesterone and oestradiol but only one had SP1 levels above the corresponding 50th centile value. As only three samples were obtained from this group no conclusions are possible.

The progesterone/oestradiol concentration ratio was calculated for each sample; there were no significant differences between the ratios in groups 1, 2 and 3 even though the five highest ratios of >20 were found in groups 2 and 3, but all three patients in group 4 had ratios of <10.

Discussion

The present study found that levels of serum hCG at between 9 and 16 weeks gestation were significantly higher in out-patients with nausea alone or nausea and vomiting than in those who were symptom free. This supports the concept that hCG might be the aetiological agent for 'morning sickness' as the maximum incidence of this condition coincides with the first trimester peak levels of hCG. Our findings agree with those reported by Schoeneck (1942) who although measuring hCG in urine by a modified Friedman test found a relation between hCG values and the extent of nausea and vomiting. We disagree with Soules *et al.* (1980) who found no relation between serum hCG levels and the incidence and severity of nausea and vomiting; that study included only 46 women and compared absolute hCG concentrations, whereas the present study of 113 women takes into account the varying gestational ages.

Fairweather & Loraine (1962) concluded that the mean urinary hCG level in women with hyperemesis gravidarum was significantly lower than that found in pregnant control patients. In our study only three samples were obtained from patients with hyperemesis gravidarum and therefore no conclusions could be drawn. Moreover, these three subjects suffered from dehydration and subsequent haemoconcentration as a consequence of hyperemesis, which was not evident in other subjects in the study and as Fairweather (1968) pointed out 'hospitalization' could have caused a reduction in hCG levels.

Circulating levels of SP1 have not been studied previously in relation to nausea and vomiting in pregnancy. As with hCG there is a rapid output of SP1 in the first trimester (Lenton *et al.* 1981) and it was therefore considered a possible causal agent of nausea and vomiting in early pregnancy. No significant differences in SP1 levels were noted.

The oestradiol results do not alter the conclusions of Shute (1938) who found clinically identical degrees of nausea and vomiting in patients with low, normal or high oestrogen values It is likely that the pregnant woman can compensate for the gradual rise in oestrogens throughout early pregnancy but the sudden administration of a high-dose oestrogen pill as a postcoital contraceptive would cause a more profound metabolic upset and this could explain the resulting sickness.

As we found no significant differences between the progesterone levels in the four groups we are not able to support the theory of Christofides *et al.* (1982) that high progesterone levels might cause nausea by inhibiting motilin. The measurement of an individual's receptor activity might be necessary to support this hypothesis. A suggestion that 'morning sickness' might be due to a difference in the ratio of oestradiol/progesterone concentrations was not supported; no significant differences were noted between the ratios found in the four groups studied.

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Immunoreactive oestrogens and progesterone in amniotic fluid in twin pregnancies

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Summary. Amniotic fluid concentrations of immunoreactive oestrogens and progesterone were measured at the time of caesarean section in 32 twin pregnancies; 25 women had an elective section and seven were in labour at the time of operation. No significant differences between concentrations in the amniotic fluid of the first and second twin were found in respect of conjugated and unconjugated oestrone, oestradiol, oestriol, oestetrol and unconjugated progesterone either before or during labour. It is unlikely that changes in oestrogens or progesterone in the amniotic fluid are responsible for the selective changes seen in prostaglandins and fetal adrenal steroid during labour in the first twin.

The ability of the oestrogens to enhance myometrial contractility has formed the basis for several hypotheses on the initiation of parturition (Thorburn & Challis 1979). Activation of the enzyme 17α-hydroxylase in the placenta of several species, such as the sheep, leads to decreased maternal circulating levels of progesterone and increased concentrations of oestrogens (Liggins *et al.* 1973; Thorburn & Challis 1979). No similar consistent observations have been made in women and the role of these steroids in human parturition remains unresolved.

There are at least three ways in which the oestrogens can influence myometrial contractility other than those reflected by changes in the maternal circulation (Turnbull *et al.* 1977, 1980). Firstly, alteration in concentrations in amniotic fluid or intrauterine tissues may be achieved locally. Secondly, significant differences may reside in the conjugated fractions in view of the very active sulphatase activity of the membranes. Thirdly, there may be changes in intra- or extra-cellular binding of the hormones which are not reflected in absolute hormone concentrations. The first two of these possibilities form the subject of this study.

We have previously shown that the twin pregnancy is a valid model in which to study human parturition (Norman *et al.* 1981, 1983*a*, *b*, 1984) and this communication reports on the amniotic fluid concentrations of immunoreactive oestrogens and progesterone in late twin pregnancy.

Patients and methods

Patients

The patients studied were seen at the twin clinic and their clinical features and reasons for caesarean section have been described previously (Norman *et al.* 1983*a*, *b*). Amniotic fluid was obtained by dual sac amniocentesis at the time of operation and stored at −20°C until assay. Twin I was defined as the fetus closest to the pelvic outlet Patients were divided into those who were delivered before the onset of labour and those delivered during active labour.

Analytical methods

Concentrations of immunoreactive oestrogens

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were measured by radioimmunoassay (RIA) following ethyl acetate extraction of the amniotic fluid. Total (conjugated and unconjugated) oestrogens were measured after enzymatic hydrolysis (Norman *et al.* 1983*a*) and the conjugated fraction calculated as the total minus the unconjugated fraction. Recovery of individual oestrogens was monitored by addition of tritiated oestrone (78±2%, mean ± SD), oestradiol (89±3%), oestriol (72±3%) and oestetrol (68±3%).

RIA agents were purchased from Radio Systems Laboratories, California (oestrone), Nordiclab, Finland (oestradiol), Amersham International UK (oestriol) and Hypolab, Serono, Italy (oestetrol). Antibody cross-reactions were as follows: oestrone (17β-oestradiol 1%, all others <0·01%), oestradiol (oestrone 0·9%, oestriol 0·3%, other steroids <0·01%), oestriol (oestetrol 31%, all other steroids <0·2%), oestetrol (all <0·2%). Assay coefficients of variations were all less than 13%

Progesterone immunoreactivity was determined by radioimmunoassay after ethyl acetate extraction (Diagnostic Products Corporation, California). The antibody cross-reacted with 20α-dihydroprogesterone (6%), desoxycorticosterone (3%), corticosterone (0·4%) and all other steroids less than 0·1% Recovery of tritiated progesterone was 90±3% and inter- and intra-assay variation was less than 11%.

Statistical analysis

Statistical differences between twins were investigated with the Wilcoxon test and between groups by the Mann–Whitney *U* test. Correlations were performed using the Spearman correlation coefficient. Differences were regarded statistically significant at $P<0·05$.

Results

Unconjugated oestrogens

Table 1 shows the concentrations of immunoreactive unconjugated oestrogens in amniotic fluid of patients delivered before and during labour. Levels of all four oestrogens were not significantly different between twins I and II, either before or during labour and there was no difference between samples obtained from patients during active labour compared with those taken before labour.

Conjugated oestrogens

Table 2 shows the concentrations of immunoreactive oestrogens in amniotic fluid. There were no significant differences between twins I and II or between groups.

Progesterone

Seventeen of 24 patients delivered before the onset of labour and five of seven delivered during labour had lower concentrations of progesterone in the first sac than in the second, but the differences were not significant ($P = 0·07$).

Relationship of steroid concentrations to gestational age at time of delivery

Both unconjugated and conjugated oestriol and

Table 1. Unconjugated immunoactive oestrogens and progesterone in amniotic fluid before and during active labour in twin pregnancies

		Before labour		Active labour	
Steroid	Twin no	Mean (SEM)	No in group	Mean (SEM)	No in group
Unconjugated oestrone (nmol/l)	I	0·97 (0·12)	25	0·93 (0·18)	6
	II	1·29 (0·25)		0·97 (0·28)	
Unconjugated oestradiol (nmol/l)	I	0·6 (0·2)	15	1·3 (0·5)	5
	II	0·8 (0·2)		1·3 (0·7)	
Unconjugated oestriol (nmol/l)	I	85 (28)	18	89±30	5
	II	106 (39)		84±60	
Unconjugated oestetrol (pmol/l)	I	71 (23)	23	29±11	5
	II	77 (37)		78±54	
Progesterone (nmol/l)	I	89 (9)	24	79±24	7
	II	102 (13)		106±7	

Table 2. Conjugated immunoactive oestrogens in amniotic fluid before and during labour in twin pregnancies

Steroid	Twin no.	Before Labour		Active Labour	
		Mean (SEM)	No in group	Mean (SEM)	No in group
Conjugated oestrone (nmol/l)	I	5·3 (0·4)	24	4·4 (0·9)	5
	II	5·9 (1·0)		4·8 (1·0)	
Conjugated oestradiol (nmol/l)	I	7 (1)	14	5 (3)	4
	II	6 (1)		3 (3)	
Conjugated oestriol (nmol/l)	I	1353 (255)	17	1922 (255)	4
	II	1180 (248)		2171 (480)	
Conjugated oestetrol (pmol/l)	I	332 (56)	20	407 (172)	4
	II	425 (86)		352 (140)	

oestetrol were positively correlated with gestational age at delivery (twin I oestriol $r = 0{\cdot}39$, $P<0{\cdot}05$, oestetrol $r = 0{\cdot}45$, $P<0{\cdot}02$; twin II oestriol $r = 0{\cdot}39$, $P<0{\cdot}05$, oestetrol $r = 0{\cdot}51$, $P<0{\cdot}2$). Conjugated oestetrol also increased with gestational age (twin I $r = 0{\cdot}42$, $P<0{\cdot}02$; twin II $r = 0{\cdot}65$, $P<0.001$). The other oestrogens did not increase significantly with gestational age.

Discussion

The results of the present study indicate that the fetal membranes and decidua are exposed to increasing concentrations of immunoreactive oestriol and oestetrol in the last weeks of gestation. No such increases in the biologically more active oestrone and oestradiol were found, nor did progesterone change significantly. There were no significant differences between amniotic fluid concentrations in twin I and those in twin II, either before or during labour for any of these steroids.

Previously we suggested that events in the lower segment of the uterus are the trigger for labour in twin pregnancies and we described differential increases in amniotic fluid glucocorticoids, prostaglandins and phospholipids in the first twin during labour (Norman *et al.* 1981, 1983*a*); cortisol, prostaglandin E and androstenedione are increased in the umbilical circulation of the first twin during labour (Norman *et al.* 1983*b*, 1984). It has been suggested that an increase in oestrogen initiates parturition (Turnbull *et al.* 1977, 1980) but no differential changes between the twins could be demonstrated in the present study. This was true of both unconjugated oestrogens and progesterone and the conjugated oestrogens. Although conjugated oestrogens probably have no biological activity, the presence of active sulphatases in the membranes may make the pool of conjugated steroids an important reservoir for the release of unconjugated oestrogens directly to the tissues in the proximity of the membranes (Turnbull *et al.* 1977).

While these findings do not exclude a role for the oestrogens and progesterone at a cellular level, it is unlikely that these steroids in the amniotic fluid play any significant role in precipitating labour by differentially altering prostaglandin production in the first sac.

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Continuous acid–base assessment of the human fetus during labour by tissue pH and transcutaneous carbon dioxide monitoring

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Summary. Simultaneous monitoring of fetal tissue pH (t-pH) and transcutaneous carbon dioxide (Tc-PCO$_2$) was performed in 30 labours. Both t-pH and Tc-PCO$_2$ at delivery were positively correlated with pH (r = 0·69) and PCO$_2$ (r = 0·68) of the umbilical artery blood. A tissue/transcutaneous standard base excess (t-SBE) was derived from the t-pH and the Tc-PCO$_2$ and calculated for 13 fetuses at delivery; there was a correlation with standard base excess of umbilical artery blood. An analysis of t-pH and Tc-PCO$_2$ changes during the last hour of labour revealed that only infants who were born with decreased pH of the umbilical artery blood had decreasing t-SBE, while all others had a constant t-SBE.

Fetal blood sampling, introduced by Saling in 1961, can determine acidosis during labour and offers a distinction between its metabolic and respiratory components. Unfortunately, it gives only intermittent information, and repeat samples are often needed. Furthermore, every collection of blood requires vaginal examination and amnioscopy.

During the last 8 years continuous tissue-pH (t-pH) monitoring has been possible with the Kontron-Roche tissue pH electrode. The t-pH is linearly correlated with both capillary and umbilical artery blood pH (Weber *et al.* 1978, Lauersen *et al.* 1979), but as the PCO$_2$ is unknown, it is impossible to decide whether an acidosis is due to hypercapnia or is metabolic.

Recently, fetal transcutaneous carbon dioxide (Tc-PCO$_2$) measurements have been reported (Thomsen & Weber 1984; Hansen *et al.* 1984). These investigations have shown very good correlation between Tc-PCO$_2$ and PCO$_2$ in samples of capillary blood and umbilical artery blood. Simultaneous continuous monitoring of the acid–base state by Tc-PCO$_2$ and t-pH measurements would elucidate the nature of the fetal acidosis during labour. This is the first report describing such monitoring of the human fetus.

Subjects and methods

After informed consent 30 women at term were included in the study. Three patients suffered from pre-eclampsia, four from rhesus isoimmunization and one from diabetes mellitus. The other 22 patients had uncomplicated pregnancies. Five patients had labour induced by prostaglandin E$_2$ pessaries, and 25 had a spontaneous labour.

The electrodes were applied when the cervical os was at least 4 cm dilated and the membranes ruptured. After sterilization and calibration (pH 7·38 and pH 6·84) the Kontron-Roche glass electrode was applied to the scalp (Flynn & Kelly 1980). The electrode was connected to a pH-meter (PHM 75, Radiometer), and the t-pH was recorded on the cardiotocograph (8030A, Hewlett-Packard). Values between 7·00 and 7·50 were recorded every 10 s (Fig. 1). After calibration at 5 and 10% CO$_2$ gas mixtures the Tc-PCO$_2$ electrode (E5230, Radiometer) was

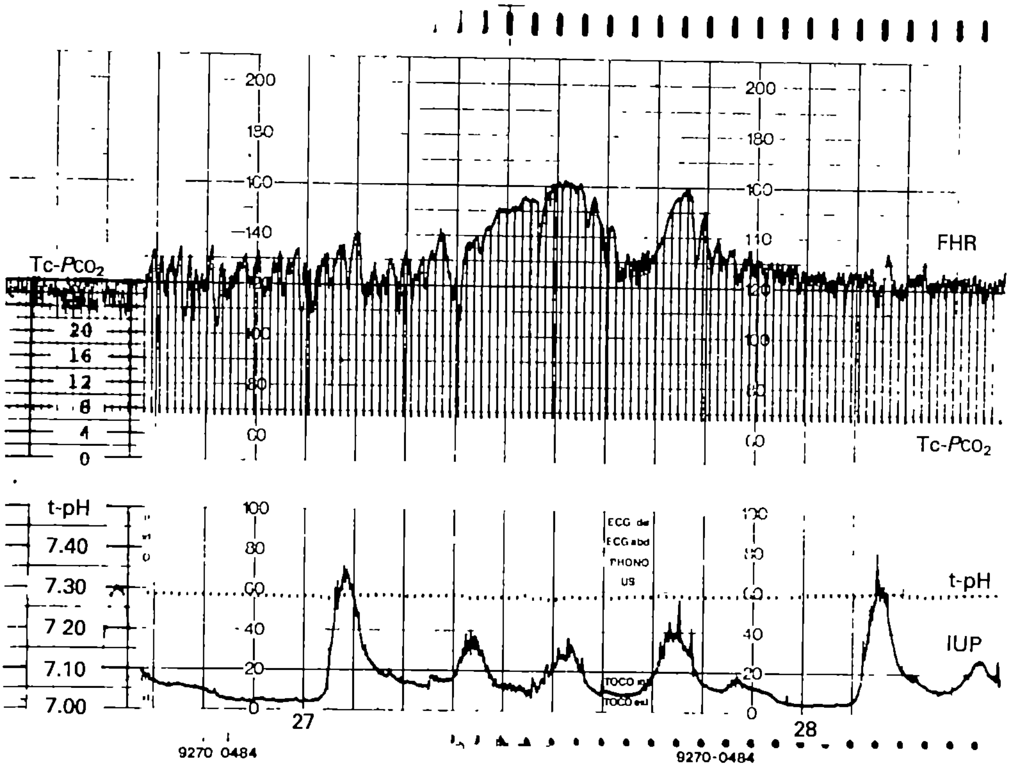

Fig. 1. Cardiotocogram with the fetal heart rate (FHR) and the transcutaneous carbon dioxide tension (Tc-Pco_2) (bottom of vertical lines) in the upper part and the intrauterine pressure (IUP) and the tissue-pH (t-pH) (dotted line) in the lower part.

sterilized by fluid aldehydes (Korsolin) and attached to the fetal scalp with a suction ring by means of a negative pressure of 20 kPa (150 mmHg) (Weber & Secher 1979). There was no preparation of the skin before monitoring, and a temperature of 44°C was chosen. The Tc-Pco_2 electrode was connected to a monitor (TCM20, Radiometer), and the values were recorded on the cardiotocograph every 10 s (Fig. 1). Decision making during labour was based on the CTG and the t-pH (Weber 1982), but not on the Tc-Pco_2.

Immediately after birth blood was collected anaerobically from the umbilical artery and vein and analysed on a blood gas analyser (ABL3, Radiometer). After each monitoring both electrodes were recalibrated to evaluate their drift.

Results

Twenty-five patients were delivered spontaneously, four by vacuum extraction because of a prolonged second stage (one) or suspected fetal hypoxia (three), and one by caesarean section because of dystocia. Although a t-pH <7·20 was usually checked by reapplication of the electrode, this procedure was not carried out in one patient, as a severe bradycardia required rapid intervention. The t-pH was 7·14, but the infant was born with normal umbilical artery blood pH (7·28) and Apgar scores of 10 at 1 and 5 min after delivery. A total of 24 t-pH monitorings were successful, which means that the monitoring was continuous even during the second stage of labour until just before delivery (Table 1). Also 24 Tc-Pco_2 monitorings were successful, but in some patients the electrode had to be reapplied during the second stage of labour as it had slipped out of the suction ring Reapplication was quick, and the same Tc-Pco_2 level was obtained in <2 min.

The drift of the t-pH electrode was 0–0·12 pH units (mean 0·035). In four patients (nos 15, 18, 26, 28) the drift was 0·09, 0·10, 0·10 and 0·12, while it was <0·04 in all the others. The Tc-Pco_2 electrode drift was 0–25% (mean 5·5%). In four

Table 1. Details of exclusions (failed recordings) of fetal tissue pH (t-pH) and transcutaneous CO_2 (Tc-$P\mathrm{co}_2$) monitorings in 30 labours

	Failed recordings		
Monitoring	*n*	Patient no	Reason for failure
t-pH (*n* = 30)	6	2	Refused further monitoring after t-pH electrode applied.
		13, 14, 24	No acceptable pH signal obtained despite electrode reapplication.
		19	Only 5 min monitoring
		20	Low t-pH not checked by reapplication
Tc-$P\mathrm{co}_2$ (*n* = 30)	6	2	Refused further monitoring
		3, 9	Technical problems with Tc-$P\mathrm{co}_2$ monitor.
		12	Loss of Tc-$P\mathrm{co}_2$ membrane during sterilisation
		19	Only 5 min monitoring
		30	Unphysiologically high Tc-$P\mathrm{co}_2$ values

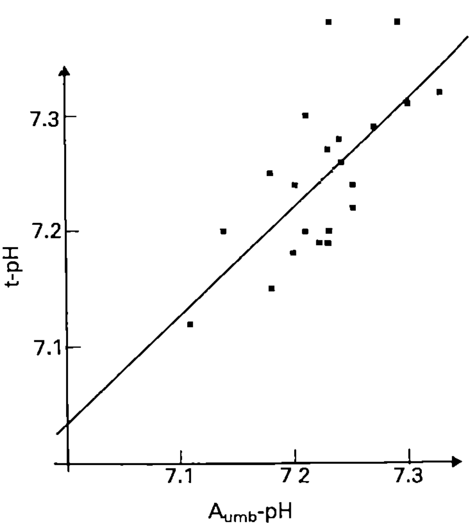

Fig. 2. Correlation between umbilical artery pH (A_{umb}-pH) and tissue pH (t-pH) at delivery. $y = 0\cdot942x+0\cdot44$; $r = 0\cdot69$; $n = 21$; $P<0\cdot001$.

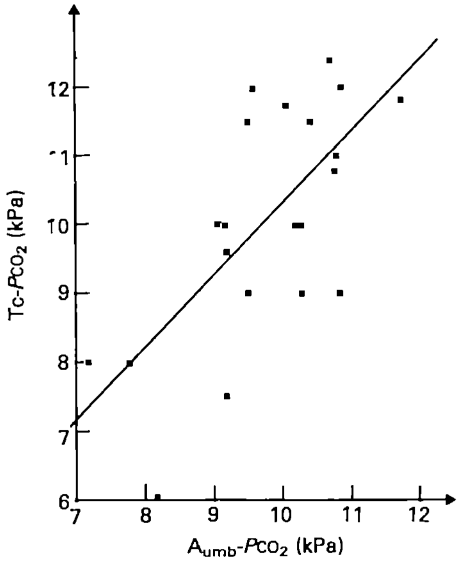

Fig. 3. Correlation between umbilical artery $P\mathrm{co}_2$ and transcutaneous carbon dioxide tension (Tc-$P\mathrm{co}_2$) at delivery. $y = 1\cdot035x-0\cdot072$; $r = 0\cdot68$; $n = 21$; $P<0\cdot001$.

patients (nos 10, 11, 14, 29) it drifted 10, 12, 25 and 25%, while the drift in all the others was <8%.

Based on the 24 successful monitorings the t-pH at delivery and the umbilical artery blood pH were positively correlated ($r = 0\cdot53$, $P<0\cdot01$). If the four patients with excessive drift were excluded, the correlation coefficient was 0·69 ($P<0\cdot001$) (Fig. 2). The Tc-$P\mathrm{co}_2$ was positively correlated ($r = 0\cdot50$, $P<0\cdot05$) with the $P\mathrm{co}_2$ of the umbilical artery blood, corrected according to the anaerobic temperature coefficient of co_2 in blood (Siggaard-Andersen 1974). Omitting the patients with drift of ≥10%, the correlation coefficient was 0·68 ($P<0\cdot001$) (Fig. 3).

The standard base excess of the umbilical artery blood (A_{umb}-SBE) was calculated from the pH and the $P\mathrm{co}_2$ by the blood gas analyser. From the t-pH and the Tc-$P\mathrm{co}_2$ corrected to 37°C, a 'tissue/transcutaneous standard base excess' (t-SBE) was calculated using the Siggard-Andersen nomogram or the formula describing the nomogram (Fig. 4). Excluding unsuccessful

$$\mathrm{SBE} = 0{\cdot}5\left(-155{\cdot}4068+\sqrt{24151{\cdot}2822-4\,\frac{24{\cdot}47-\mathrm{HCO_3}(40)}{0{\cdot}005624}}\right)$$

$$\mathrm{HCO_3}(40) = 1{\cdot}224\times10^{\left(\frac{\mathrm{pH}(40)-6{\cdot}161}{0{\cdot}9524}\right)}$$

$$\mathrm{pH}(40) = \frac{5{\cdot}6512-\mathrm{pH}}{3{\cdot}9168-\mathrm{Log}\,P\mathrm{co_2}}\,(1{\cdot}6021-\mathrm{Log}\,P\mathrm{co_2})+\mathrm{pH}$$

Fig. 4. Formula for calculation of standard base excess (SBE). Pco_2 is carbon dioxide tension in mmHg at 37°C SBE is expressed in mmol/l (Siggard-Andersen 1974).

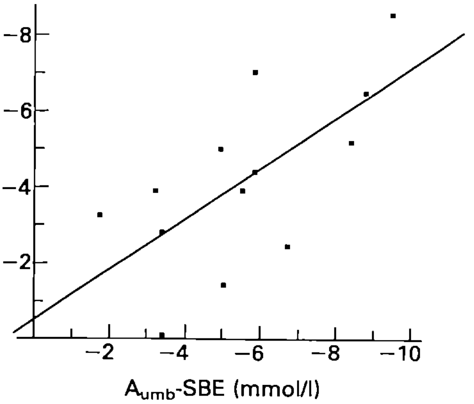

Fig. 5. Correlation between standard base excess of the umbilical artery blood (A_{umb}-SBE) and 'tissue/transcutaneous standard base excess' (t-SBE) at delivery. $y = 0{\cdot}664x-0{\cdot}519$; $r = 0{\cdot}66$; $n = 13$; $P<0{\cdot}05$.

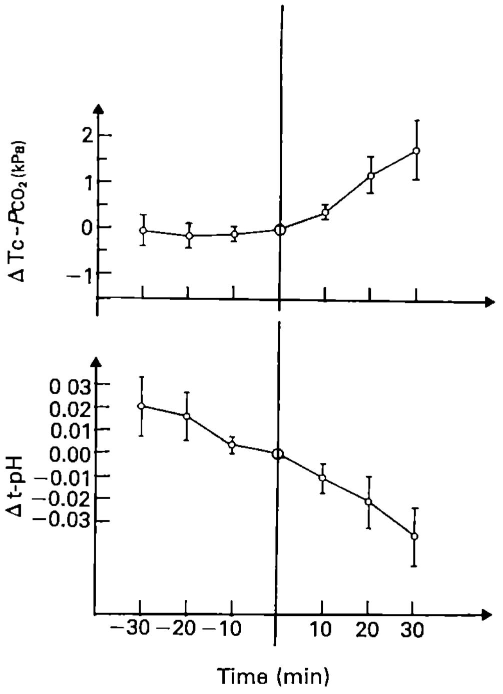

Fig. 6. Changes (mean±SEM for every 10 min) in t-pH and Tc-Pco_2 during the last 30 min of the first stage and the first 30 min of the second stage of labour (n = 12–20).

recordings and the patients with excessive drift, the remaining 13 patients showed a correlation between the t-SBE and the A_{umb}-SBE ($r = 0{\cdot}66$, $P<0{\cdot}05$) (Fig. 5).

As pH values <7·20 are often considered pathological (Bowe *et al.* 1970), only patients who gave birth to a baby with umbilical artery pH of >7·20 were regarded as normal. In these patients the mean t-pH and Tc-Pco_2 at the start of the second stage of labour were respectively 7·30 (SEM 0·02) and 8·49 (SEM 0·40) kPa at 44°C. Beginning at the start of the second stage of labour, changes in t-pH (Δt-pH) and Tc-Pco_2 (ΔTc-Pco_2) were calculated for each of these patients during the last 30 min of the first stage and the first 30 min of the second stage (Fig. 6). The t-pH decrease during the last 30 min of the first stage was not accompanied by any Tc-Pco_2 increase. Consequently, t-SBE was decreasing until the beginning of the second stage. During the second stage the Tc-Pco_2 increase was pronounced and despite the t-pH decrease, the calculated t-SBE increased to the same level as that at 30 min before the second stage. The Δt-pH and ΔTc-Pco_2 of two fetuses who at delivery had umbilical artery blood pH measurement of 7·11 and 7·14 respectively are illustrated in Fig. 7. The calculated t-SBE was decreasing even during the second stage of labour. Consequently, the t-pH decrease in these patients could not be explained by CO_2 accumulation alone.

Discussion

In previous studies of t-pH monitoring the suc-

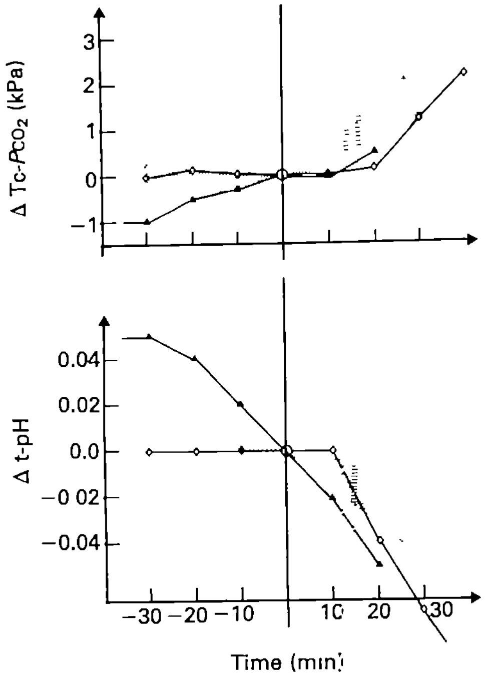

Fig. 7. Changes in t-pH and Tc-$P\text{co}_2$ in two fetuses delivered with $\mathrm{A_{umb}}$-pH <7·20. ◇ Case no. 8; ▲ case no. 11

cess rates were 50–80% (Weber 1980). The Kontron-Roche electrode with 'round shoulders' used in our study is easier to handle than previous models but still carries a 20% failure rate, the main difficulty being dislocation of the tip of the electrode. This causes the measuring point of the electrode to slip out of the incision and the pH to decrease to unphysiological values. The construction of the electrode, with the measuring point directly in the open skin incision, makes it difficult to avoid this problem, but when the electrode is correctly applied, several studies have shown a close correlation between t-pH and both capillary (Lauersen *et al.* 1979) and umbilical artery blood pH (Sturbois *et al.* 1977) of the fetus. The four recordings with an excessive electrode drift were probably caused by insufficient calibration before monitoring.

In contrast, the Tc-$P\text{co}_2$ electrode is very simple to apply by suction fixation. Previous studies of Tc-$P\text{o}_2$ have documented that the suction ring does not interfere with the measured value, when compared with glue fixation (Weber & Secher 1979). As heating and perfect contact between the skin and the electrode is less essential in Tc-$P\text{co}_2$ monitoring than in Tc-$P\text{o}_2$ monitoring (Frederiksen *et al.* 1984), the suction fixation is justified. In all cases with excessive drift of the Tc-$P\text{co}_2$ electrode the same 1-year-old electrode had been used. Since this electrode was discarded, the drift has been acceptable.

Knowing the $P\text{co}_2$ and the pH of blood, the base excess can be calculated by nomogram or formula (Siggard-Andersen 1974). The base excess, defined as the difference in concentration of strong base between the blood and the same blood titrated with strong acid or base to pH 7·40 and $P\text{co}_2$ 40 mmHg at 37°C, is the negative value of the amount of nonvolatile acid, mainly lactic acid. Whereas the actual base excess is an in-vitro estimation on blood, the standard base excess is the in-vivo counterpart depending on the buffering capacity of the whole extracellular fluid compartment (including the interstitial fluid). The use of standard base excess eliminates the influence of small variations in the haemoglobin concentration.

The linear correlations of t-pH and Tc-$P\text{co}_2$ to pH and $P\text{co}_2$ of blood or extracellular fluid suggest a correlation between the standard base excess calculated from transcutaneous and tissue values and the standard base excess calculated from blood values. This assumption is corroborated by the correlation (r = 0·66, P<0·05) found between t-SBE and $\mathrm{A_{umb}}$-SBE. Consequently, simultaneous monitoring of t-pH and Tc-$P\text{co}_2$ enables us to distinguish between intrapartum acidosis caused by hypercapnia and acidosis originating from hypoxia and the formation of lactic acid. The relevance of this distinction is based on previous animal studies (Bruns 1963; Myers 1972) which concluded that metabolic acidosis with lactic acid formation is more dangerous in causing brain damage than respiratory acidosis.

Beard & Morris (1965), using fetal scalp blood samples, found that the mean fetal pH declined significantly during labour from 7·28 (SEM 0·05) at the start of the second stage to 7·24 (SEM 0·06) at delivery. In the same series $P\text{co}_2$ rose from 40 mmHg (5·3 kPa) to 44 mmHg (5·9 kPa) (SEM not mentioned). This modest rise in $P\text{co}_2$ was not sufficient to explain the pH decline, and consequently Beard & Morris (1965) found a decreasing base excess in their 26 patients during the second stage of labour. At the start of the second stage Weber & Hahn-Pedersen (1979) in normal fetuses found a mean t-pH of 7·30 (SEM 0·07) and a decline of 0·12 pH units/h. In the present study the mean t-pH and the decline during the second stage are consistent with previous studies, but the mean Pco_2 (6·05 kPa at 37°C) as well as the Pco_2 increase during second stage were higher. During the first stage of labour we found a less pronounced pH decrease just as described by Beard & Morris (1965) and by Weber & Hahn-Pedersen (1979). The t-pH decrease, in spite of the constant Tc-Pco_2, during the last part of the first stage of labour (Fig. 6) could be explained by maternal hyperventilation, as the decreased maternal CO_2 may induce peripheral vasoconstriction (Saling 1984) and decreasing tissue and capillary pH with only minimal central blood pH changes.

In our study two patients, who gave birth to babies with A_{umb}-pH of <7·20, had decreasing t-SBE, but the 'normal' patients had unchanged t-SBE during the last hour of labour, corroborating the conclusion of a previous study of Tc-Pco_2 (Thomsen & Weber 1984). One of the patients with A_{umb}-pH of <7·20 had constant values of t-pH, Tc-Pco_2 and t-SBE during the first 10 min of the second stage, but then a rapid decline in t-pH and a declining t- SBE occurred. The infant had Apgar scores of 7 and 10 at 1 and 3 min after birth. The second patient demonstrated declining t-pH during the last 30 min of the first stage, but because of rising Tc-Pco_2 there was no decline in t-SBE until the start of the second stage. The newborn had Apgar scores of 9 and 10 at 1 and 5 min after delivery.

Although our number of patients is limited, it seems that the combination of continuous pH and Pco_2 estimations of the fetus during labour is superior to either of the two estimations alone, as this monitoring discriminates between a dangerous metabolic acidosis and a less severe respiratory acidosis (Myers 1972). A metabolic acidosis should always indicate intervention, while a slight respiratory acidosis might be treated conservatively. At present this monitoring method should be reserved for scientific purposes, but as soon as better t-pH electrodes are available, routine clinical use will be possible.

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Risk factors associated with small-for-dates and large-for-dates infants

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Summary. Relative risks were calculated to assess the potency of different factors associated with the two extremes of the birthweight distribution. Maternal height affected the chances of having a small-for-dates (SFD) or large-for-dates (LFD) baby to an equal and opposite extent; but the risks associated with maternal weight were greater for LFD than SFD infants. Smoking increased the SFD risk by 3·5 times, whereas the LFD risk was only reduced by a half. Pre-eclampsia was associated with a very high SFD risk (14·6); in the LFD group it was insignificantly raised. The LFD relative risk steadily rose with increasing parity, but in the SFD group it fluctuated around unity. Among multiparae the risks of an SFD or LFD infant when previous siblings had been of relatively low or high birthweight for gestational age, respec tively, were much increased. Estimates of attributable risk showed that if pathological factors such as smoking, hypertensive disorders and congenital abnormalities could be completely eliminated the number of SFD babies in this population would be reduced by about 60%; conversely the number of LFD babies would be increased by about 30%.

Analyses of data from the British Birth Surveys of 1958 and 1970 (Peters *et al.* 1983) showed that major factors associated with the birthweight of infants were maternal height, history of smoking in pregnancy, parity and history of pre-eclampsia during pregnancy. With the large number of cases involved, and the fact that the magnitude of the associations had changed little in the course of 12 years, these findings can be taken as conclusive. But shifts in mean birthweight are of little relevance to the practising obstetrician. His main concern is directed at the two extremes of the birthweight range where perinatal problems are much increased. Extrapolation from effects on mean values to other parts of the distribution can be misleading. A shift in mean birthweight may, for instance, be due to a factor exerting more, or all, of its influence at one extreme and little, or none, at the other. On the other hand a factor which only affects the spread of the distribution will make no difference to the mean value but would increase (or decrease) the proportions at both extremes. For clinical purposes it is therefore important to investigate the relative potency of different variables at the two extremes of the birthweight range. Do very short and very tall women, for example, have equal chances of having small-for-dates (SFD) and large-for-dates (LFD) babies, respectively? How is the parity effect manifested at the extremes of birthweight? To what extent (if any) does the absence of severe pre-eclampsia enhance the likelihood of an LFD infant?

Some of the confusion about the origins of SFD and LFD babies arises because of the confounding of two different viewpoints, the clinician, who wants to know the relative potency of different factors in individual patients; and the epidemiologist, who wants to know the contribution made by each factor to the SFD or LFD population as a whole. Estimates of 'relative' and 'attributable' risk magnitudes can be used in parallel to meet the requirements of these opposing points of view. We have already made separate analyses of SFD and LFD risk factors by this means (Scott *et al.* 1981, 1982). In the present study these two extreme groups are examined in parallel, so that the relative potency of different factors can be compared and contrasted.

Patients and methods

During the years 1964 to 1977 women giving birth to small-for-dates (SFD) and large-for-dates (LFD) babies in Oxford hospitals were personally interviewed within 3 days of delivery and their babies examined by medical members of a small research team. The criteria were that their birthweights should be >2SD below or above the mean, respectively, for gestational age and sex, as defined by the British Perinatal Mortality survey (Butler & Alberman 1969). Only those who were sure of their dates, with a regular cycle not exceeding 32 days, and whose last menstrual period was not a withdrawal bleed from the pill were included. Women in the adjacent beds who gave birth to average-for-dates (AFD) babies whose birthweights were all within 2SD of the mean for gestational age and sex were included as a comparison group. Their numbers were fewer since entry to this group did not begin until the study had been in progress for several years. The social class, maternal age and parity distributions, and the proportion of instrumental deliveries and caesarean sections among the women in this group did not differ from those for all Oxford hospital births in 1972 (Jean Fedrick, personal communication). All the infants in the study were white European singleton births.

Variables

Using an original data base comprising 1392 pregnancies, maternal factors for which the SFD or LFD groups differed from the AFD group at a significance level of 1% or less were selected for analysis. After adjustment for confounding between variables it was found that eight maternal factors were associated with an increased risk of having either an SFD or LFD baby or both. They were used in the present study. Major congenital abnormalities were also included since many affected babies have associated intra-uterine growth retardation. The definitions and criteria for these factors were as follows. Maternal height was measured by the midwife at the first antenatal visit. Pre-pregnancy weight was reported by the patient at personal interview. Net pregnancy weight gain was calculated by subtracting pre-pregnancy, fetal and placental weight from the final weight. The means of the birthweights for gestational age of previous live-born siblings were set against the same standards as the index cases (Butler & Alberman 1969) and their position in standard deviations above or below the mean recorded. Women were said to be hypertensive if a blood pressure of ≥140/90mmHg was recorded at any time during pregnancy. Definite proteinuria on at least two occasions was necessary before moderate or severe pre-eclampsia was diagnosed. All these patients were also hypertensive as defined above. Women with mild pre-eclampsia only were included in the normotensive category Smokers regularly smoked at least one cigarette per day. With the exception of siblings birthweight, the cut-off points for continuous variables were taken in standard deviations around the AFD mean. The present analyses are made on 532 SFD, 371 AFD and 479 LFD mother-infant pairs for whom valid data were available for all the nine variables.

Statistical methods

Relative risks provide a simple means of assessing the potency of different factors in individual patients. In this study they are used to estimate the proportionate increase (or decrease) in the risk of an SFD or LFD pregnancy associated with each factor. Thus with a relative risk of 2·0 the chances are doubled and with a value of 0·5 they are halved. Relative risk estimates have a skewed distribution, and therefore the usual method of representing accuracy in terms of standard errors is inappropriate. For this reason 95% confidence limits are given (Armitage 1971). Their spread gives an indication of accuracy, and the estimate is significant if the confidence limits are entirely below, or above, the value 1; i.e. do not traverse unity.

It is also important to assess the contribution of different factors to the SFD or LFD populations as a whole. However high its associated risk, a factor will have little impact if its prevalence is low. Various indices of 'attributable risk' have been created to supply this need (Walter

1976). In the present analyses the 'etiologic fraction' (Levin 1953) has been used. This statistic estimates the proportionate reduction in cases that would occur if the risk factor or its effects were eliminated.

Some factors, such as maternal age and parity, are closely linked Associations between short stature, smoking and social class (Butler & Alberman 1969) and between smoking and pre-eclampsia (Golding & Adelstein 1980) have also been found. Account therefore needs to be taken of these relationships. All the estimates given here were obtained by the use of a 'linear logit model' which automatically adjusts for confounding between variables (Armitage 1971). They therefore represent the 'net' effect of each factor, independent of its association with the other variables.

Results

Using the AFD group as a basis for comparison the relative risks (rr) of being SFD or LFD associated with different factors were estimated. The findings are shown in Table 1. In order to facilitate comparison the inverse of the relative risk (l/rr) is also given for the LFD group. Smoking during pregnancy more than trebled the chance of a woman having an SFD baby, whereas the likelihood of an LFD baby was halved. Hypertension had only a marginal effect. The presence of moderate or severe pre-eclampsia increased the risk of SFD pregnancy 15-fold; and the risk of LFD pregnancy was also slightly, but insignificantly, raised. Primiparity did not increase the risk of an SFD baby, but parous women were more than twice as likely to have LFD babies. When the birthweight for gestational age of previous siblings had been below the mean the risk of an SFD pregnancy was markedly increased, and the birth of an LFD baby was extremely unlikely. Maternal height had a similar (but opposite) effect at both extremes of the birthweight range, but maternal weight had a marginally greater effect in association with LFD than SFD babies. On the other hand below average net pregnancy weight gain doubled the chances of having an SFD baby whereas it had no effect on the risk of having an LFD baby. The risk of being SFD when the baby was congenitally abnormal was markedly increased, and the risk of being LFD was also slightly, but insignificantly raised.

Graduated relative risk estimates are given in Table 2. Heavy smoking clearly increases the chances of having an SFD baby, but the LFD risk changes little according to the amount smoked. The findings for hypertension and pre-eclampsia reflect those in Table 1, and show increased risks of having SFD babies, particularly when the mother has pre-eclampsia, but little association with having an LFD infant. Maternal parity did not seem to affect the chances of having an SFD baby, but there was a steady increase in the LFD risk with rising parity. Our data clearly show the predictive value of the previous siblings' birthweight on a proband pregnancy, and the relative risk of an LFD baby when previous siblings had been relatively heavy was higher than that of an SFD baby when previous siblings had been relatively light. Maternal height had an equal and opposite effect at the two extremes of the birth-

Table 1. The relative risks of being small-for-dates or large-for-dates associated with different factors[*]

	Small-for-dates	Large-for-dates	
	rr	rr	1/rr
Smoking (or not)	3·5 (2·6–4·8)	0·5 (0·3–0·7)	2·1 (1·5–3·1)
Hypertension (*vs* normotension)	2·7 (1·8–4·0)	0·8 (0·5–1·2)	1 3 (0·8–1·9)
Pre-eclampsia (*vs* normotension)	14·6 (5·8–36·5)	1·7 (0·6–5·0)	0·6 (0·2–1·8)
Primiparity (*vs* multiparity)	1·2 (0·9–1 6)	0·4 (0·3–0·6)	2·3 (1·7–3·1)
Siblings birthweight (<standard mean)	5·7 (3·2–10·1)	0·1 (0·0–0·1)	13·1 (7·9–21·5)
Maternal height (<AFD mean)	1·3 (1·0–1·9)	0·7 (0 5–1·0)	1·5 (1·0–2·1)
Maternal weight (<AFD mean)	1·7 (1·2–2·5)	0·4 (0·3–0·6)	2·5 (1·8–3·6)
Net pregnancy weight gain (<AFD mean)	2·1 (1·5–3·0)	0·9 (0·6–1·2)	1·1 (0·8–1·6)
Congenital abnormality (or not)	11·5 (3·6–36·9)	2·7 (0·7–10·4)	0·4 (0·1–1·4)

95% confidence limits are given in parentheses.

[*] In each case adjustment has been made for all the other variables.

Table 2. Graduated relative risks related to different factors*

Smoking		Non-smoker	<10 per day		>10 per day
	SFD	1·0	2·8 (1·8–4·2)		3·9 (2·6–5·8)
	LFD	1·0	0·5 (0·3–0·9)		0·4 (0·2–0·7)
Hypertension/pre-eclampsia		Normotensive	Hypertensive		Pre-eclamptic
	SFD	1·0	2·9 (2·0–4·4)		18·7 (7·2–48·5)
	LFD	1·0	0·6 (0·4–1·0)		1·0 (0·3–2·9)
Parity		0	1	2	≥3
	SFD	1·0	0·8 (0·5–1·1)	1·0 (0·6–1·7)	0·7 (0·4–1·2)
	LFD	1·0	1·7 (1·2–2·4)	2·1 (1·3–3·3)	4·4 (2.6–7·4)
Congenital abnormality		Normal	Major CA		
	SFD	1·0	14·1 (4·4–45·1)		
	LFD	1·0	1·9 (0·5–6·8)		
		Standard deviations around the mean (as in Table 1)			
		<−1 SD	± 1 SD		>+1 SD
Siblings birthweights					
	SFD	7·0 (4·1–12·1)	1·0		0·5 (0·1–1·6)
	LFD	0·2 (0·1–0·6)	1·0		12·8 (7·1–23·2)
Maternal height					
	SFD	2·0 (1·3–3·0)	1·0		0·9 (0·5–1·5)
	LFD	0·8 (0·5–1·4)	1·0		1·6 (1·1–2·5)
Maternal weight					
	SFD	1·8 (1·2–2·8)	1·0		0·8 (0·5–1·5)
	LFD	0·2 (0·1–0·5)	1·0		2·9 (1·9–4·6)
Net pregnancy weight gain	SFD	1·6 (1·0–2·5)	1·0		0·3 (0·1–0·5)
	LFD	0·8 (0·5–1·4)	1·0		1·5 (0·9–2·4)

95% confidence limits are given in parentheses.
*In each case adjustment has been made for all the other variables.

weight range; but the risk of having an LFD baby was greater when the mother was heavy than that of having an SFD baby when the mother was light. It is interesting to note also that the relative risk of an SFD baby in a heavy mother was close to unity, whereas that of an LFD baby in a light mother was nearer to zero. The reverse occurred when net pregnancy weight gain was examined· the chances of a woman with a high weight gain having an SFD baby were very low, but low net pregnancy weight gain only slightly decreased the risk of an LFD baby.

Attributable risks corresponding to the relative risks in Table 2 are shown in Table 3 The total estimates for the discrete variables are included; but for the continuous variables they are obviously dependent on the cut-off points selected, and have therefore been omitted Smoking makes a contribution of over 40% to the SFD population as a whole, and the proportion is higher for heavy than moderate smokers. Hypertension, with or without pre-eclampsia also contributes 28·4%, and because of its greater prevalence the estimate for hypertension alone is greater than that for pre-eclampsia. Multiparity makes a contribution of 40% in the LFD group. Little change is found with increasing parity, since the rising risk is balanced by a fall in the number of women at higher parities. The contribution of siblings' birthweights is high in both groups, and the estimates for maternal height, weight and weight gain reflect the relative risk values for these factors.

Discussion

All the women in this study were delivered in Oxford, where the levels of health, housing, employment, and obstetric care are above the national average. With adverse social and pathological factors reduced to a minimum, biological variables might be expected to show higher associations with fetal size and outcome than in less well favoured communities. However, the

Table 3. Graduated attributable risks related to different factors*

Smoking		Non-smoker	<10 per day		>10 per day	Total
	SFD	0·0	15·6		24·8	40·4
	LFD	0·0	−7·7		−11·6	−19·3
Hypertension/pre-eclampsia		Normotensive	Hypertensive		Pre-eclamptic	Total
	SFD	0·0	17·7		10·7	28·4
	LFD	0·0	−9·4		−0·1	−9·6
Parity		0	1	2	3 or more	Total
	SFD	0·0	−6·8	0·4	−4·3	−10·7
	LFD	0·0	13·5	8·6	18·0	40·0
Congenital abnormality		Normal	Major CA			Total
	SFD	0·0	6·3			6·3
	LFD	0·0	0·9			0·9
		Standard deviations around the mean (as in Table 1)				
		<−1 SD	±1 SD	>+1 SD		
Siblings birthweight						
	SFD	25·6	0·0	−1·1		
	LFD	−4·5	0·0	−41·0		
Maternal height						
	SFD	15·0	0·0	−1·2		
	LFD	−1·6	0·0	11·9		
Maternal weight						
	SFD	13·0	0·0	−2·0		
	LFD	−7·7	0·0	25·7		
Net pregnancy weight gain						
	SFD	9·7	0·0	−13·2		
	LFD	−3·5	0·0	6·3		

Results are percentages

*In each case adjustment has been made for all the other variables

four main factors associated with birthweight in the National Surveys of 1958 and 1970 (Peters *et al* 1983) are also prominent here. Our preliminary analyses had shown significant differences between the SFD and AFD groups for social class distribution, and between the LFD and AFD groups for maternal age, but as in the National Surveys their effects virtually disappeared when account was taken of confounding variables such as maternal size, smoking habits and parity. Diabetes mellitus is also, in general, associated with the birth of babies of above average weight. The diagnosis was made in two SFD, one AFD and nine LFD pregnancies. The LFD relative risk was 7·0, but this value did not achieve significance, and because of the low prevalence of the disease the attributable risk (1·6%) was negligible. It is clear that diabetes mellitus makes only a small contribution to LFD pregnancies as a whole.

When one considers the effect of individual factors in the two extreme groups different patterns emerge. Maternal stature seems to exert its influence fairly smoothly throughout the birthweight range Pre-pregnancy weight, as reported by the mother, is a less reliable measure than height (recorded by the midwife); and net pregnancy weight gain will be dependent on the gestational age achieved at delivery The risk values for these two variables should be viewed with this in mind, but some differences are apparent Maternal weight has a slightly larger effect than maternal height, and the relative risk of an overweight mother having an LFD baby is greater than that of a light woman having an SFD baby. The risk of an LFD infant when net weight gain is low was only slightly reduced, but an SFD infant is very unlikely in association with relatively high weight gain. These three factors have been examined in greater detail elsewhere (Ounsted & Scott 1981).

Parity and moderate to severe pre-eclampsia exert their influence almost exclusively at one extreme of the birthweight range. With increasing parity the risk of having an LFD baby steadily rises, whereas that for an SFD baby remains fairly constant. This suggests that the restriction of fetal size associated with primiparity affects mainly those fetuses of average or above average weight. The presence of pre-eclampsia markedly increases the chance of having an SFD baby, but no significant association was found with LFD infants.

One factor not included in the analyses of Peters *et al.* (1983) is the birthweights of previous siblings. High correlations between the birthweights of siblings were shown many years ago (Donald 1939; Karn *et al.* 1951) and our earlier demonstration that some women regularly have very small or very large babies (Ounsted 1965, 1966) has been amply confirmed by more recent studies (Ounsted & Ounsted 1973; Bakketeig *et al,* 1979). Butler (1974) noted that the birthweight of previous babies was a particularly good indicator of intrauterine growth retardation among multiparae since in 39% women having a SFD baby a previous baby weighed ≤2·5 kg. Using the same data bank but a less severe criterion for SFD Adelstein & Fedrick (1978) found that if three or more previous babies had weighed ≤2·5 kg the risk was 5·9 times that in the total population. Bakketeig *et al.* (1979), in their extensive study of siblings birthweights and gestational ages in Norway, showed that mothers of LFD first births had a relative risk of 3·0 of repeating an LFD second birth; and there was a cumulative risk in the third birth given that both of the first two births were of similar outcome.

Our data show strong associations with siblings' birthweights in both extreme groups; but the risks for the LFD group were even larger than those for the SFD group Our AFD group was used to calculate these estimates, and although these index cases were normally distributed about the standard mean with the exception of the two tails (Ounsted *et al.* 1983*a, b*) the distribution of their siblings was non-symmetrical: 60% were below and 40% above the mean. This apparent distributional incongruity may have arisen by chance; but it could be due, in part at least, to the parity effect (Peters *et al.* 1983). Since all these babies were by definition earlier born than the index cases a generalized shift towards lower birthweight for previous siblings in the AFD group would be expected. This might account for the relatively higher risk estimates for the LFD compared with the SFD group.

It is important to compare and contrast the relative and attributable risks within groups since the interpretation of these two measures of risk is different, and neither is a substitute for the other. This is particularly relevant when considering SFD pregnancies The relative risks associated with pre-eclampsia and congenitally abnormal babies were high, but because these pathological factors are fairly uncommon their contribution to the SFD population as a whole is small. On the other hand maternal smoking increased the relative risk to a much lower extent, but because of its high prevalence (57% of the mothers in this group smoked) its contribution to SFD pregnancies as a whole is very large It was probably confusion over these different aspects which misled earlier attempts to allocate the 'suggested percentage distribution of causes of small-for-dates babies in the United Kingdom' (Dawes 1974).

It is clear that pathological factors make a large contribution to SFD pregnancies. If smoking, hypertension, pre-eclampsia and congenital abnormalities could be prevented the number of SFD babies in this population would be reduced by about 60%. The risks associated with smoking alone contribute largely to this; and their magnitude is twice as great at the lower compared with the upper extreme of the birthweight distribution. Among biological factors maternal height has an equal and opposite effect, but the attributable risk associated with overweight LFD pregnancies was double that associated with lightness in SFD pregnancies. The greatest difference, however, is that due to parity. Multiparity made a very high contribution in LFD pregnancies (40%), whereas the attributable risk associated with primiparity in the SFD group (10·7%) was not significant. Finally, it should be noted that the relative and attributable risks associated with siblings' birthweights remain high after adjustment for confounding variables. This indicates that the regularity with which many women repeatedly have SFD or LFD babies is independent of these other factors.

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Maternal azathioprine therapy and depressed haemopoiesis in the babies of renal allograft patients

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Summary. Maternal immunosuppression with azathioprine during pregnancy can depress fetal haemopoiesis resulting in neonatal thrombocytopenia and leucopenia with the potential for serious sequelae. The effect on the infant of adjusting azathioprine dosage on the basis of maternal total leucocyte count has been studied in 10 pregnancies in eight renal allograft recipients. Throughout the first six pregnancies azathioprine dosage was unchanged and although the characteristic pregnancy leucocytosis was evident it was not maintained in four patients whose leucocyte counts by 32 weeks gestation were significantly less than our norm [10·3 (SD 1·7) $\times 10^9$/l] and who subsequently had babies with cord leucocyte counts $\leqslant 8{\cdot}0 \times 10^9$/l, again significantly less than our norm [13·7 (SD 3·9) $\times 10^9$/l]. A significant correlation existed between maternal leucocyte counts at 32 weeks gestation and at delivery and cord leucocyte count ($r=0{\cdot}847$; $P<0{\cdot}01$ and $r=0{\cdot}915$; $P<0{\cdot}01$ respectively). Three of these infants had platelet counts $\leqslant 100 \times 10^9$/l but there was no correlation between maternal platelet counts at 32 weeks gestation or at delivery and cord platelet count. For the next four pregnancies policy changed: at 32 weeks gestation azathioprine dosage was halved if maternal leucocyte count was at or below the 1SD band ($8{\cdot}6 \times 10^9$/l) for normal pregnancy. All of the infants were haemotologically normal and two patients whose first babies had leucopenia and thrombocytopenia had second babies without problems. Analysis of data from all 10 pregnancies still demonstrated a significant correlation between cord leucocyte count and maternal leucocyte count at delivery but no longer at 32 weeks gestation. It is concluded that in pregnant renal allograft recipients adjustment of azathioprine dosage so as to maintain maternal total leucocyte count within normal physiological limits for pregnancy avoids neonatal leucopenia and thrombocytopenia.

Thymic atrophy, leucopenia, anaemia, thrombocytopenia, chromosome aberrations in lymphocytes, reduced immunoglobulin levels, infections and septicaemia have been reported as specific complications in babies of renal allograft recipients as well as problems associated with preterm delivery and intrauterine growth retardation (Davison & Lindheimer 1984). These are the hazards faced by a baby conceived and grown in a chronically immunosuppressed environment, although many of the side-effects of azathioprine (imuran), the most

Table 1. Immunosuppressive drugs, infant data and some haematological data for eight renal allograft patients studied during 10 pregnancies

	Immunosuppressive drugs		Infant				Leucocyte count (×10⁹/l) Maternal			Platelet count (×10⁹/l) Maternal		
No.	Aza (mg/day)	Pred (mg/day)	Gestation (weeks)	Sex	Weight (kg)	Cord Hb (g/dl)	Week 32	Delivery	Cord	Week 32	Delivery	Cord
1A	100	10	36	F	3·61	15·9	8·1	7·9	8·0	180	180	20
B	100	10	39	F	3·52	16·1	8·6	11·0	10·0	200	175	250
2A	100	10	37	M	2·36	14·4	7·9	7·4	1·6	190	100	20
B	100	10	36	F	2·23	18·1	8·1	10·0	13·0	200	190	235
3	150	10	38	M	2·57	16·9	8·6	8·7	6·4	130	95	100
4	100	7·5	36	F	2·27	14·9	8·4	8·7	6·7	300	280	200
5	150	10	37	M	2·69	17·0	11·6	10·5	11·6	300	300	165
6	50	5	32	M	1·60	17·3	10·8	10·9	13·0	300	300	150
7	100	7·5	37	M	3·89	15·1	8·6	10·0	11·5	250	270	170
8	100	10	38	F	1·94	14·8	10·3	11·0	15·0	300	300	280

Aza, Azathioprine (dosage was halved at 32 weeks gestation in 1B, 2B and 7). Pred, prednisone.

frequently used immunosuppressant, are not necessarily aspects of immunosuppression but are related to its inherent cytotoxic activity (Barber 1981).

Depressed haemopoiesis with thrombocytopenia and/or leucopenia has the potential for serious sequelae. The ability to predict some weeks before term which babies are likely to be affected could influence the method of delivery; better still, it might allow reduction of maternal azathioprine dosage before delivery to enable fetal haemopoiesis to recover. Experience with pregnant patients who have immunological thrombocytopenic purpura has revealed no relation between maternal and cord platelet counts (PLC) and therefore maternal platelet counts do not provide a sufficiently disciminating basis for management (Ayromlooi 1978; Scott *et al.* 1980, 1983; Cines *et al.* 1982; Logaridis *et al.* 1983; Morgenstern *et al.* 1983). Whether or not maternal white cell count (WCC) has some discriminating value in the pregnant renal allograft patient has never been assessed even though serial white cell counts have been used in clinical practice to monitor myelosuppression in these patients. We have analysed the data from our small series of pregnant transplant patients and have assessed the effect of adjusting maternal azathioprine dosage on neonatal white cell and cord platelet counts to determine whether maintaining maternal white cell counts within the normal pregnant range (Taylor & Lind 1976) influences the cord blood counts.

Subjects and methods

Eight renal transplant recipients have been studied in 10 pregnancies (Table 1). All patients were taking immunosuppressive drugs: pred-

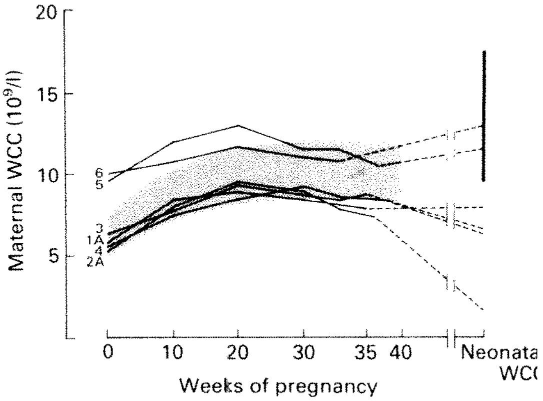

Fig. 1. Serial maternal total white cell counts (WCC) throughout pregnancy in 6 women with renal transplants (solid lines). Corresponding neonatal total white cell counts are shown linked to the respective pregnancies. The shaded area and the heavy vertical line represent the 1SD band for normal pregnancy and newborn infants respectively. Patient designation shown on the left side of the figure corresponds to that used in Table 1.

nisone ≤10 mg/day and azathioprine ≤2 mg/kg body weight/day. None of the mothers or offspring had clinical or serological evidence of active cytomegalovirus (CMV) infection.

Haematological assessments of maternal venous blood using a Coulter Counter (Model S-Plus) were performed at 2-weekly intervals up to 32 weeks gestation and weekly thereafter. (One baby—No. 6—was delivered at 32 weeks). At delivery blood samples were obtained from the mother and the umbilical cord. All blood samples were put into standard sequestrene tubes and analysed within 3 h except those from overnight deliveries which were stored at 4°C until analysed the next morning.

Results

First six pregnancies (numbers 1A, 2A, 3, 4, 5 and 6)

These mothers were delivered before we realized the extent of the problem of depressed fetal haemopoiesis. Pre-pregnancy azathioprine and prednisone dosages were therefore maintained unchanged throughout pregnancy. The initial leucocytosis characteristic of normal pregnancy was evident in all cases (Fig. 1). In four of the pregnancies (1A, 2A, 3 and 4), however, the increment in total white cell count was not sustained and by 32 weeks gestation counts were at

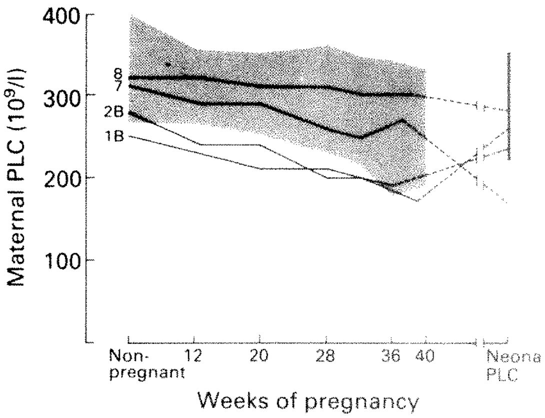

Fig. 2. Serial maternal platelet counts (PLC) throughout pregnancy in six women with renal transplants (solid lines). Corresponding neonatal platelet counts are shown linked to the respective pregnancies. The shaded area and the heavy vertical line represent the 1 SD band for normal pregnancy and newborn infants respectively. Patient designation shown on the left of the figure corresponds to that used in Table 1.

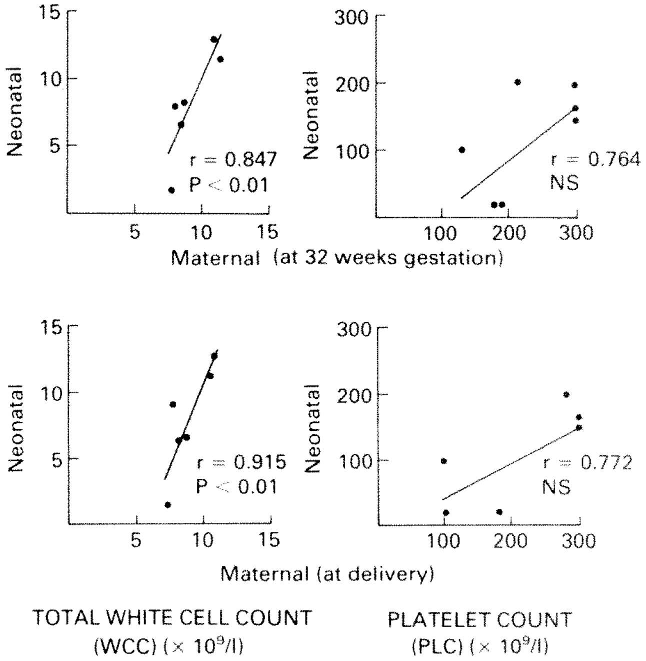

Fig. 3. Relationship between maternal total white cell and platelet counts (at 32 weeks gestation and delivery) and neonatal total white cell and platelet counts, calculated by linear regression analysis. Six pregnancies nos. 1A, 2A, 3, 4, 5 and 6.

or below the 1SD band (8·6×10⁹/l) for normal pregnancy (8·1, 7·9, 8·6 and 8·4×10⁹/l respectively). At delivery the four babies had cord leucocyte counts of 8·0, 1·6, 6·4 and 6·7×10⁹/l respectively [norm 13·7 (SD 3·9) ×10⁹/l]. Three of these babies (1A, 2A and 3) had decreased cord platelet counts at 20, 20 and 100×10⁹/l respectively [norm 185 (SD 65) ×10⁹/l] (Fig. 2). These three mothers had platelet counts at 32 weeks that were below the 1SD band for our normal population [280 (SD 65) ×10⁹/l] [All norms from Taylor & Lind (1976) and T. Lind, unpublished data].

Maternal leucocyte and platelet counts remained relatively unchanged between 32 weeks gestation and delivery (average of 4·8 weeks, excluding the baby born at 32 weeks). Linear regression analysis revealed a significant correlation between maternal leucocyte counts at 32 weeks gestation and at delivery and cord leucocyte count. There was no significant correlation between cord and maternal platelet counts (Fig. 3).

In all six patients maternal erythrocte count and haemoglobin concentration remained constant during the second half of pregnancy [4·09 (SD 0·7) ×10⁹/l and 10·9 (SD 0·9) g/dl respectively at 32 weeks gestation] although mean cell volume was higher than for our normal population [94·3 (SD 5·2) fl *vs* 86·6 (SD 4·1) fl]. At delivery cord haemoglobin concentrations were within normal limits (see Table 1).

Next four pregnancies (nos. 1B, 2B, 7 and 8)

In the light of the experience with the first six pregnancies we changed our policy, albeit on an empirical basis. It was decided that if at 32 weeks gestation maternal white cell count was at or below the 1SD band (8·6×10⁹/l) for normal pregnancy then azathioprine dosage would be halved. Azathioprine dosage was reduced on this basis in three patients (nos. 1B, 2B and 7). The average time to delivery was 5 weeks during which maternal white cell count increased on average by 22% but maternal platelet count remained unchanged (Figs 4 and 5). The cord leucocyte and platelet counts in these three infants (and the one born to the patient whose therapy was not reduced) were within normal range. Two of the patients, whose first babies (1A and 2A) had been leucopenic and thrombocytopenic, had second babies without haematologcal problems.

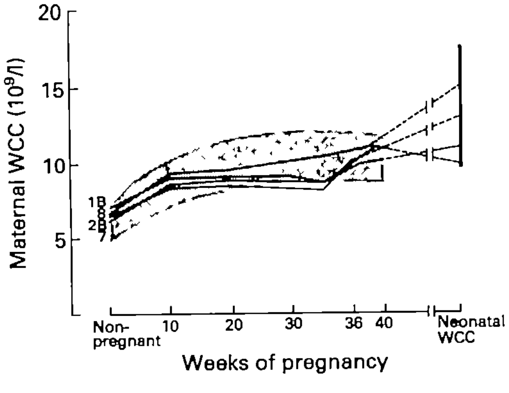

Fig. 4. Serial maternal total white cell count (WCC) throughout pregnancy in four women with renal transplants (solid lines) Corresponding neonatal total white cell counts are shown linked to the respective pregnancies. The shaded area and the heavy vertical line represent the 1 SD band for normal pregnancy and newborn infants respectively. Patient designation shown on left side of figure corresponds to that used in Table 1 In three of the pregnancies (1B, 2B and 7) maternal azathioprine dosage was halved at 32 weeks gestation.

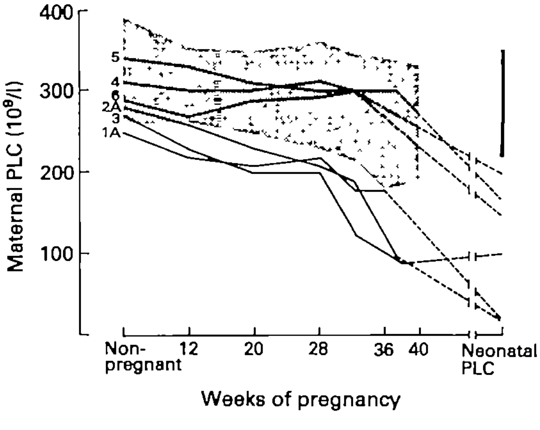

Fig. 5. Serial maternal platelet count (PLC) throughout pregnancy in four women with renal transplants (solid lines) Corresponding neonatal platelet counts are shown linked to the respective pregnancies. The shaded area and the heavy vertical line represent the 1 SD band for normal pregnancy and newborn infants respectively. Patient designation shown on left side of figure corresponds to that used in Table 1. In three of the pregnancies (1B, 2B, and 7) maternal azathioprine dosage was halved at 32 weeks gestation

Linear regression analysis of the pooled data from all 10 pregnancies still showed a significant correlation between maternal leucocyte count at delivery and cord leucocyte count (Fig. 6). However, there was no longer a significant correlation between maternal leucocyte count at 32 weeks gestation and cord leucocyte count presumably because reduction of azathioprine at 32 weeks in pregnancies 1B, 2B and 7 had altered subsequent maternal and fetal leucocyte counts relative to each other. Again, there was no significant correlation between maternal platelet count at 32 weeks and delivery and cord platelet count.

Four of the ten babies (2A, 2B, 4 and 8) were below the 10th centile of birthweight for gestation (Thomson *et al.* 1968).

Discussion

This limited study has demonstrated that adjusting azathioprine therapy in pregnant renal allograft patients on the basis of maternal leucocyte count can prevent neonatal leucopenia and thrombocytopenia. This management was formulated after analysing our initial experience against the background of haematological data for normal pregnancy documented in Newcastle (Taylor & Lind 1976; Taylor *et al.* 1982; T. Lind, unpublished data) and comparable with those obtained elsewhere (Sejeny *et al.* 1975; Wallenburg & Van Kessel 1978; Pitkin & Witte 1979). In retrospect we realized that three of the first six babies had unknowingly been jeopardized because of leucopenia and thrombocytopenia: 2 of them (1A and 2A), had platelet counts of $20\times10^9/l$, well below the critical level of $50\times10^9/l$ when there is a significant risk of intracranial haemorrhage (Scott *et al.* 1980).

From the literature it was not apparent that depressed haemopoiesis would be such a problem for the newborn infants as very few data were given about the cord blood profiles (Davison & Lindheimer 1984) and often the word 'normal' was used without qualification. Based on our initial experiences and that of others (Gevers *et al.* 1971; Jacob *et al.* 1974; Leb *et al.* 1971; Price *et al.* 1976; Rasmussen *et al.* 1981; Sciarra *et al.* 1975) it was decided to institute management based on empirical reduction of azathioprine dosage after 32 weeks gestation if maternal total leucocyte count was $8{\cdot}6\times10^9/l$ or

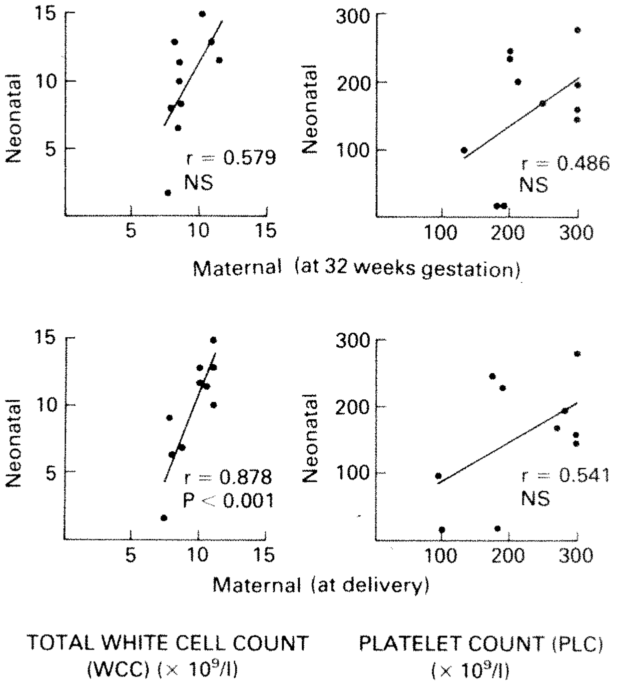

Fig. 6. Relationship between maternal total white cell and platelet counts (at 32 weeks gestation and delivery) and neonatal total white cell and platelet counts, calculated by linear regression analysis. All ten pregnancies.

less. In deciding on this approach several other facts were taken into consideration. (a) Azathioprine is metabolized to the purine antagonist 6-mercaptopurine (6-MP), whose maximum effect takes several days to appear and persists for up to a week after dosage is reduced (Barber 1981). (b) Isotope-labelled azathioprine (^{35}S-azathioprine) is readily transferred to the fetus, with fetal blood levels being between 64 and 93% of maternal levels within 24 h (Saarikoski & Seppälä, 1973; Levy 1981; Williamson & Karp 1981). (c) Leucopenia and occasionally thrombocytopenia occur in many non-pregnant renal transplant patients because the usual dose of azathioprine (2–3 mg/kg body weight/day) straddles the level at which myelosuppression occurs (Strom *et al.* 1981). (d) Kinetic studies have shown that the leucocyte production cycle is biphasic (5–10 days of proliferation followed by 3–10 days of maturation) and that the lifespans of different leucocytes vary with a few days for granulocytes and monocytes but up to a year for lymphocytes (Ford 1974; Vincent 1974). (e) The platelet production cycle is 3–5 days with a platelet lifespan of 8–12 days (Hardisty 1974; Wallenburg & Van Kessel 1978), although in pregnancy platelet kinetics are more complex because of increased platelet consumption (hyperdestruction) especially during the third trimester (Fay *et al.* 1983). (f) The exact time-scale of fetal haemopoiesis is not known but it probably does not differ greatly from the adult except that the major site is in the liver up to 28 weeks before the bone marrow predominates, with the spleen contributing to lymphopoiesis (Lewis 1974).

Therefore allowing for the pharmacokinetics of azathioprine, the time-scale for production and delivery of new leucocytes and platelets into the blood and the fact that reduction of azathioprine dosage in the non-pregnant adult allows haemopoietic recovery within 1–2 weeks it was thought that our plan was at least theoretically sound and should be tested. It was assumed that the influence of steroid therapy haemopoiesis would have long since attained a steady state; moderate granulocytosis with minimal eosinopenia and lymphopenia being the major quantitative effects (Ford 1974).

The practice of adjusting azathioprine dosage empirically on the basis of maternal myelosuppression requires more detailed investigation. Further information is needed about the effect on differential leucocyte count and changes in blood levels of azathioprine and its metabolites, particularly 6-MP. However, changes in blood metabolite levels may be irrelevant because the most useful index of bioavailability and effectiveness of treatment is red cell 6-thioguanine nucleotide (6-TG nucleotide), a metabolite of both azathioprine and 6-mercaptopurine (Herber *et al.* 1982). This may provide the most sensitive method of monitoring the effects of altering azathioprine dosage.

It should be noted that what little information we have relates almost entirely to the effects of azathioprine and with the introduction of the new immunosuppressive agent cyclosporin A (which appears to be more effective than conventional immunosuppression) new assessments will be needed. Interestingly at least 10 'successful and completely uncomplicated pregnancies with babies of birthweight appropriate for gestational age' have been reported to the pharmaceutical company which supplies cyclosporin A, although we are aware of only one published report (Lewis *et al.* 1983).

Four of the 10 babies reported in our study had birthweights less than the 10th centile (Thomson *et al.* 1968), endorsing the experience in the literature that the incidence of small-for-gestational-age babies in renal allograft recipients is well above average (Davison & Lindheimer 1984). The severity of the renal impairment, vascular disease or hypertension does not seem to be involved and it has been postulated that non-specific depression of the maternal immune system during pregnancy can cause intrauterine fetal growth retardation (Scott 1977).

Clearly there is an urgent need to assess properly the rationale and implications of immunosuppressive regimens in renal allograft patients during pregnancy. As well as the immediate problems of neonatal thrombocytopenia and leucopenia, septicaemia and low birthweight, attention should also be focused on monitoring the remote effects on the offspring.

Acknowledgments

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Ultrasound Doppler flow studies of the ovarian and uterine arteries

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Summary. The feasibility of studying ovarian arterial blood flow has been demonstrated, using an ultrasonic method combining real-time imaging and pulsed Doppler (the 'duplex' method). Results using a percutaneous full-bladder technique were validated by comparison with use of an ultrasound probe applied directly to the arteries at laparotomy. The ovarian arteries demonstrated qualitatively and quantitatively distinct flow patterns compared with the internal and external iliac arteries. From recorded waveforms a pulsatility index (PI) reflecting vascular impedance was calculated. The PI was found to be lower, indicating increased blood flow, in the artery supplying the ovary carrying the dominant follicle or corpus luteum. Serial studies suggest that this change occurs at an early stage of the menstrual cycle, possibly before the dominant follicle can be recognized by its size or increased hormone production. Uterine arterial flow was also detectable, more accurately abdominally than vaginally, and the changes typical of late pregnancy were already found to be present, though to a lesser degree, in the first trimester.

Ultrasound has revolutionized the study of human embryology allowing serial studies of the developing fetus from an ovarian follicle to term gestation. Thus, ultrasonic imaging has provided a unique method for the non-invasive study of reproductive structural changes. In contrast, Doppler ultrasound has potential to study patterns of blood flow and hence identify functional change.

Doppler ultrasound is a non-invasive technique for investigating blood flow which has an established clinical role in the assessment of vascular disease, particularly in the vessels of the leg and neck (Atkinson & Woodcock 1982). Until recently the use of this method for the examination of flow in specific deep vessels has been difficult, since conventional continuous-wave flowmeters provide confusing signals from flow or tissue movement occurring anywhere along the entire length of the ultrasound beam. The availability of pulsed-Doppler instruments has made it possible to sample signals at a chosen depth and thus to detect flow in any selected deep vessel. Pulsed Doppler combined with real-time ultrasound imaging, the so-called 'duplex' method, allows the precise localization of a deep vessel and the positioning of the Doppler sample volume within it. The duplex technique has been used to detect blood flow in the human fetus (Eik-Nes *et al.* 1980) but its potential application in the study of normal pelvic blood flow has not yet been fully explored. The

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purpose of this study is to examine the feasibility of obtaining such signals and to investigate ways in which flow signals might change under physiological conditions.

Subjects and methods

Various groups of subjects were studied. The main group consisted of 45 subjects scanned on a single occasion without reference to the time of the menstrual cycle, for cross-sectional analysis. This group consisted of 14 healthy student volunteers (not using oral contraception) and 31 infertile but otherwise normal patients receiving no treatment. None had known cardiovascular or peripheral vascular disorder. Another three such patients were studied as a separate group because they were receiving clomiphene therapy (although unknown to the authors at the time because they were taking part in a double-blind placebo-controlled trial). A further group of three healthy student volunteers were studied serially through the menstrual cycle.

The primary studies involved recording the Doppler waveforms from the iliac, ovarian and uterine arteries through the anterior abdominal wall (percutaneous' studies). The findings were validated by employing a transducer closely applied to each artery at open surgery or through the vaginal fornices ('invasive' studies).

The invasive studies were performed on young women patients undergoing routine laparotomy, mostly for tubal surgery or hysterectomy, at the Bristol General Hospital. Transvaginal uterine artery recordings were also made from patients undergoing vaginal termination of pregnancy.

Percutaneous studies

ATL Mk 300 and Mk 600 3 MHz duplex scanners in the Vascular Studies Unit of the Bristol Royal Infirmary were used. The high-pass filter of the flowmeter eliminated Doppler shifts below 100 Hz. An on-line spectrum analyser (Angioscan) was used to give a grey-scale display of the direction and spectra of the return signals. Both the directional and non-directional signals were recorded together with the real-time image on video tape. A practical technique was gradually developed, initially for the iliac and ovarian arteries and later also for the uterine arteries, and the success rate for obtaining the Doppler signals improved as the study progressed.

Percutaneous duplex technique

The common iliac arteries were located on the real-time sector scan below the bifurcation of the aorta. Using the full bladder technique, the internal iliac vessels could be traced along the side wall of the pelvis, often lying deep to the ovary. The cursor indicating the position of the Doppler sample volume was located within the lumen of the internal iliac artery, about 2 cm distal from its origin (Fig. 1*a*).

The external iliac artery was identified immediately above the inguinal ligament and the ultrasound beam directed up into the abdomen to sample the Doppler signal. Attempts to sample from this vessel looking down into the leg resulted in the recording of flow which almost certainly originated from the profunda femoris artery.

Doppler signals from the ovarian artery were the most difficult to obtain. The artery originates from the mid-aorta and reaches the lateral aspects of the ovary through the infundibulopelvic ligament where it can often be seen clearly. When it could not be visualized on the real-time image the Doppler sample volume was moved across the ligament and then through the substance of the ovary until an arterial signal was obtained (Fig. 1*b*).

To study the uterine artery the Doppler sample volume was located immediately lateral to the cervix with the scan in a parasagittal plane. It was possible to detect blood flow towards the probe in the ascending uterine artery (Fig. 2*a*). At a slightly lower position, flow away from the probe was noted, presumably in a vaginal branch of the uterine artery (Fig. 2*b*).

Invasive recordings

Signals were obtained using a transducer applied directly to the iliac, ovarian and uterine arteries at laparotomy, and to the uterine arteries through the lateral vaginal fornices immediately before laparotomy in these patients as well as in others during early pregnancy undergoing therapeutic abortion. A 10-MHz directional continuous-wave (CW) flowmeter with no imaging facility was used with a hand-held pencil probe sterilized using low-temperature formaldehyde and steam. Clear vascular signals were easily obtained and recorded. Heterodyned directional and non-directional Doppler signals were recorded on separate channels on a tape

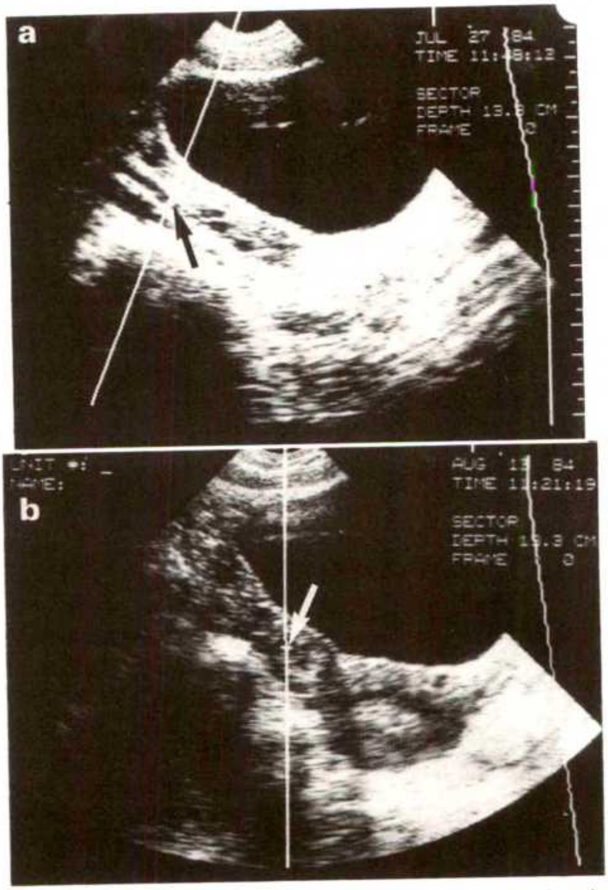

Fig. 1. Ultrasonic duplex examination of the pelvis showing the Doppler sample volume (arrowed) situated in (*a*) the internal iliac artery and (*b*) the substance of the ovary.

recorder. Real-time spectral analysis provided a visual display which helped to optimize the orientation of the probe.

Signal analysis

The signals were reviewed from the videotape using off-line spectral analysis and a photographic copy taken of spectra from three consecutive cardiac cycles of each signal. The time-velocity variation of the maximum Doppler shift frequency was then traced by hand around these three waveforms. The time-velocity waveforms were digitized using a microcomputer which then estimated a number of variables for each waveform, calculated their mean value over the three cardiac cycles, and recorded these data along with the digitized waveforms onto a magnetic disc.

The measurement of flow volume in such small vessels is not at present possible using ultrasound. The estimation of flow velocity is dependent on knowledge of the angle between the ultrasound beam and the vessel direction, and this angle is often difficult to measure in the smaller vessels. There are, however, angle-independent descriptors of the pulsatile waveform of the maximum frequency envelope and these have been shown to reflect vascular impedance distal to the point of measurement (Woodcock *et al.* 1974). One such descriptor is the pulsatility index (PI). This is defined by

$$\mathrm{PI} = (\mathrm{A} - |\mathrm{B}|)/\mathrm{mean}$$

(see Fig. 3 for explanation). Thus, if the proximal conditions remain constant and the distal vascular bed constricts, distal impedance will

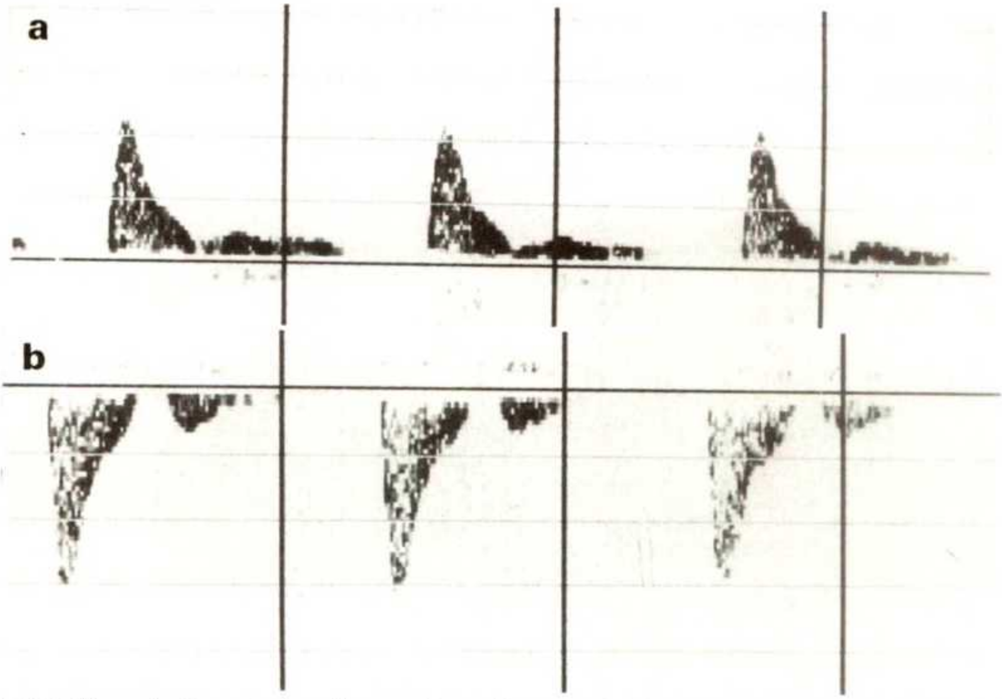

Fig. 2. (*a*) Time-velocity spectra from the ascending uterine artery with the sample volume adjacent to the cervix. Note that the waveform is above the zero line, indicating flow towards the probe. (*b*) With the Doppler sample volume position slightly deeper than in (*a*), an arterial signal is obtained which is below the zero line indicating flow away from the probe in the vaginal branch of the uterine artery. Vertical divisions: 500 Hz, horizontal divisions: 1 s.

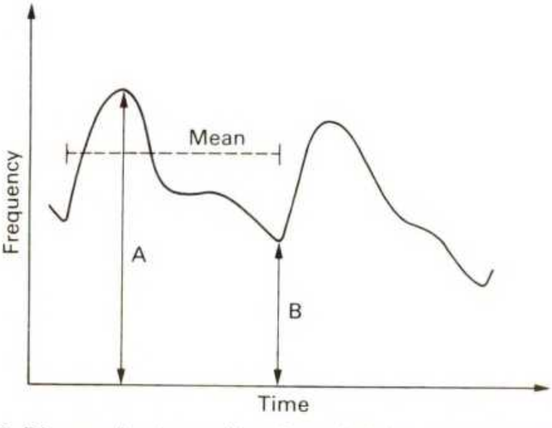

Fig. 3. Diagram showing outline of a typical time-velocity spectrum (maximum frequency envelope) illustrating the derivation of the pulsatility index (PI). PI = (A−|B|)/mean, where A is the peak systolic and B the end diastolic Doppler shift frequency. The mean is of the maximum Doppler shift frequency taken over the cardiac cycle.

increase, and the consequent reduction in flow will be reflected in an increased PI.

Results

Percutaneous studies

In the cross-sectional study on 45 normal subjects a signal could not be elicited from the ovarian artery in 12 (27%). Some of these failures were due to problems with the equipment, others because of obesity. The PIs measured in each vessel are shown in Fig. 4. The mean PI for the ovarian artery (1·58, SD 0·54, $n = 33$) was significantly lower (Student's t-test) than that for the internal iliac artery (2·81, SD 0·93, $n = 28$, $P<0·001$) or the external iliac artery (5·59, SD 2·74, $n = 24$, $P<0·001$). These findings confirmed the strong subjective impression gained during scanning that each vessel had its own characteristic waveform. Typical examples of waveforms for the internal iliac and ovarian arteries are shown in Figs 5*a* and 6 respectively.

It was noted that within the range observed for the ovarian artery the PI for the ovary containing the dominant follicle or corpus luteum was lower, the waveform lacking pulsatility (Fig. 6*a*), than for the inactive ovary, which had a waveform typical of a high impedance vasoconstricted state (Fig. 6*b*). The serial studies suggested a difference between the two ovaries which commenced early in the menstrual cycle, as demonstrated, for example, in Fig. 7. By contrast, patients treated with clomiphene typically developed multiple follicles bilaterally and both ovarian arteries showed low pulsatility waveforms typical of low impedance.

Invasive studies

Comparison of the percutaneous and invasive waveforms, illustrated by the examples from an internal iliac artery shown in Fig. 5*a* and *b* respectively, demonstrates that these are

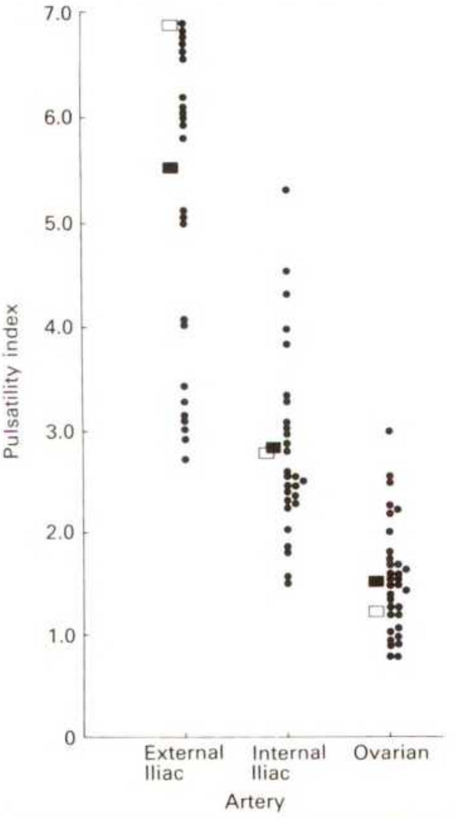

Fig. 4. Individual values of PI for the external and internal iliac and ovarian arteries by the percutaneous method. The means (■) are also shown, and compared with the means of the values obtained using the invasive method (□).

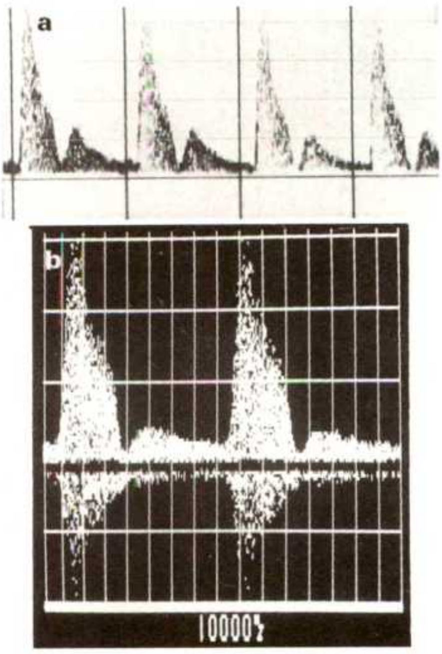

Fig. 5. Internal iliac artery waveforms obtained (*a*) percutaneously at 3 MHz (vertical markers: 500 Hz, horizontal markers: 1 s) and (*b*) by the invasive method at 10 MHz (vertical markers: 1000 Hz, horizontal markers: 125 ms). The higher Doppler shift in (*b*) is due to the higher ultrasonic frequency. However, the shapes of the waveforms are similar and the PI is virtually identical (Fig. 4).

derived from the same vessel, allowing for the difference in Doppler shift due to the difference in insonating frequency. The PI is independent of the insonating frequency. Thus, PIs for the internal iliac and ovarian arteries are similar whether measured percutaneously or directly ('invasively') as shown in Fig. 4. The somewhat higher mean PI for the exteral iliac artery measured at operation may be due to the expected peripheral vasoconstriction in the lower limb under the surgical conditions. In any case, there can be no confusion with the ovarian artery waveform.

The uterine arterial signals obtained through the lateral vaginal fornix in patients with first trimester pregnancies demonstrated the first signs of enhanced diastolic flow which characterizes the pattern in late pregnancy (Trudinger *et al.* 1983). Using the CW Doppler device it was found possible to obtain recordings from adjacent vessels, which had to be avoided with special care, whereas the percutaneous pulsed-Doppler duplex technique allowed better anatomical localization of the uterine artery.

Discussion

These studies demonstrate the feasibility of studying blood flow in the ovarian and uterine arteries by a non-invasive method using a trans-abdominal ultrasonic method combining real-time imaging and pulsed Doppler, the so-called 'duplex' method. Although it is not possible to measure flow volume a comparable index of flow can be obtained enabling study of serial changes in an artery and differences between paired arteries. The technique therefore appears to offer great potential for physiological and pathophysiological studies on the ovary and in early pregnancy.

The invasive studies enabling direct application of the transducer to the artery confirmed the accuracy of the percutaneous method, which allowed more accurate sampling of the uterine artery than the transvaginal method. Recordings from the iliac arteries were mainly useful in demonstrating the distinctive differences in flow waveforms between closely adjacent vessels, particularly the ovarian artery. These arterial 'signatures' are also helpful when attempting to identify them during pregnancy, when their anatomical positions are likely to be different. It is also of interest to note the wide range of pulsatility index (PI) values of the external iliac artery, which almost certainly reflects normal

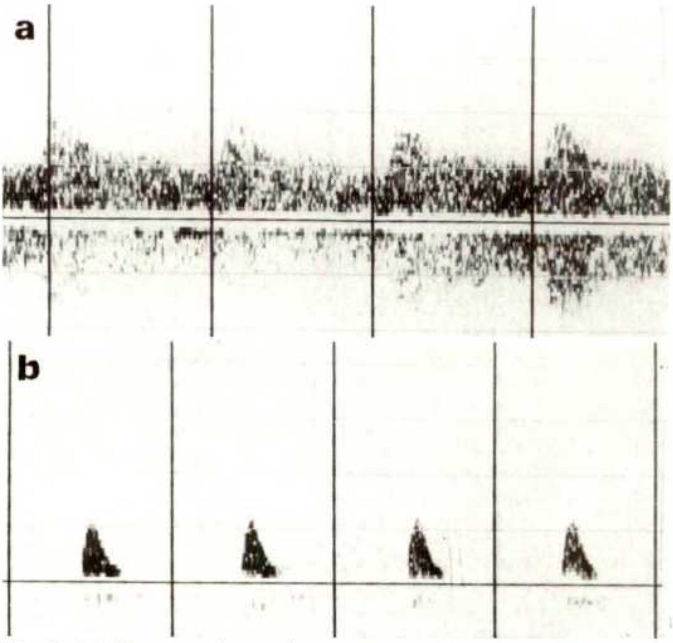

Fig. 6. (*a*) Waveform in ovarian artery on side with corpus luteum. Relatively high diastolic flow and low pulsatility is consistent with vasodilation. (*b*) Waveform from the other, 'inactive' ovary. Note absence of diastolic flow, consistent with a higher distal vascular impedance.

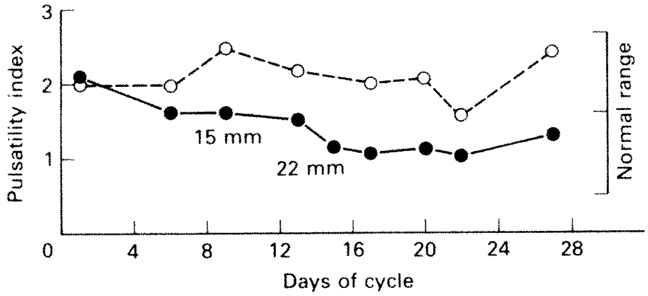

Fig. 7. Pulsatility index—reflecting vascular impedance—in the arteries to the two ovaries through a menstrual cycle. The ovary with the dominant follicle ('active' ovary) is indicated by closed circles, and the size of the follicle is given in millimetres until the corpus luteum (CL) appeared following ovulation. The normal range is from the data shown in Fig. 4 (mean ± 2 SD).

variations in lower limb impedance.

The marked difference in PI between the internal and external iliac and ovarian arteries (Fig. 4) confirms the hypothesis that the waveform in these vessels is controlled by the receiving vascular bed. The difference in PI between the two ovarian arteries depending on the presence of a dominant follicle or corpus luteum is of particular interest. Note that although Doppler shifts below 100 Hz are not displayed by this duplex instrument, this cannot be responsible for the apparent absence of diastolic flow in the ovary not containing the corpus luteum. End-diastolic Doppler shifts in the ovary with the developing follicle are typically over five times the threshold of the lowest detectable frequency (Fig. 6*a*). Longitudinal study through the menstrual cycle (Fig. 7) suggests that decreased vascular impedance, implying increased flow, occurs at an early stage of the menstrual cycle, possibly before the dominant follicle can presently be recognized by other methods. From differences in ovarian venous hormone levels in rhesus monkeys the presence of the dominant follicle is evident before it can be recognized by its size (diZerega & Hodgen 1981). Doppler ultrasound may provide a more sensitive technique which is also readily applicable in women to detect when the dominant follicle is selected. It may also help to elucidate the pathophysiology of luteal phase defects, which may have various causes, although most evidence points to inadequate development of the follicle before ovulation (diZerega & Ross 1981).

Previous studies have indicated a very low impedance in the uterine artery in late pregnancy (Trudinger *et al.* 1983). This contrasts with the high impedance waveform seen in non-pregnant women in our study. We also showed that the first signs of this change occurred early in the first trimester. It has been speculated that changes in uterine artery waveform may precede the onset of clinically apparent complications of pregnancy (Campbell *et al.* 1983). Our findings now suggest the possibility of studying early pregnancy failure in this way.

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Hormonal studies in women with premenstrual tension

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Summary. Serum hormone concentrations were determined at intervals during the last 17 days of the menstrual cycle in 35 patients with premenstrual tension (PMT) and 11 control subjects without symptoms. The maximum mean concentration of oestradiol occurred 17 days before menstruation in the patients and 14 days before in the controls. The maximum concentrations of progesterone were similar in the two groups but the mean concentrations rose earlier in the cycle in the patients with PMT. These results suggested that the patients tended to ovulate earlier in the cycle than the controls and on the basis of the ovulatory surge in gonadotrophins two groups could be identified, group A who showed signs of ovulation 14 days or less before menstruation (17 patients, 9 controls) and group B who ovulated more than 14 days before menstruation (18 patients, 2 controls). There were no significant differences between the groups in prolactin, thyroid stimulating hormone or testosterone levels, but cortisol concentrations were uniformly higher in both groups of patients compared with those in the controls. Follicular growth was assessed with ultrasound in 18 patients and 16 control subjects. Mean follicular diameters were significantly lower in the patients than in the control group at the time of ovulation. Oestradiol determinations done at the same time correlated with the diameters and were also significantly lower in the patient group. The results suggest that ovulation tends to occur prematurely in women with PMT.

Reid & Yen (1981) have reviewed in depth studies on the hormonal changes in women suffering from premenstrual tension (PMT). Since by definition the symptoms recur cyclically, it is not surprising that most attention has been paid to those hormones which show regular changes during the menstrual cycle, notably progesterone and oestrogens (Bäckström *et al.* 1976; Munday *et al.* 1981). Premenstrual symptoms of bloating, abdominal distension and peripheral oedema are among the most common complaints and although salt and water retention has been suspected to occur, few studies have been reported on aldosterone, renin–angiotensin or antidiuretic hormone (O'Brien *et al.* 1979, 1980; Munday *et al.* 1981). There have been several studies reported on prolactin, a hormone affected by stress and which interferes with menstrual function when serum levels are elevated (Andersen *et al.* 1977; Andersch *et al.* 1979, O'Brien & Symonds 1982).

Despite some early reports to the contrary, these investigations have failed to demonstrate any dramatic hormonal abnormalities in the syn-

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drome, beyond suggestions that the oestrogen/progesterone ratio is raised slightly in some women in the last week of the cycle and that progesterone is raised in others at the beginning of the luteal phase.

Psychological disturbances account for many of the symptoms and it has been suggested that some of the peptides originating from the brain, hypothalamus and elsewhere may play a part. In view of the involvement of endogenous opiates, serotonin and dopamine etc. in pituitary hormone release it has been suggested that defects in the secretion of these compounds may account not only for some of the symptoms but also for the slight abnormalities of the hormone patterns found (Halbreich & Endicott 1981; Reid & Yen 1981; Butt *et al.* 1983).

In the belief that events in the luteal phase are dependent on follicular development and ovulation earlier in the cycle, we investigated several hormones during the late follicular phase as well as in the luteal phase in women with PMT, in addition to ultrasound scanning of the ovarian follicles. Body weight measurements were also recorded. A preliminary account of the hormonal studies was reported by Butt *et al.* (1983).

Patients and methods

Patients complaining of PMT were given diary cards to complete over two cycles. Daily records were kept of the most common physical and psychological symptoms (Table 1) for which a grading system ranging from 0 (no symptoms) to 5 (most severe) was used. During the second month blood samples (30 ml) were taken at regular intervals for hormone analyses. Patients were included in the investigations only if their symptoms showed a cyclical variation with the severest symptoms in the luteal phase. Each cycle was divided into four parts, the first 7 days (week 1), day 8 after menstruation until 15 days before the next menstruation (week 2), days 14 to 8 before menstruation (week 3) and the last 7 days of the cycle (week 4). The daily scores for each symptom were summed for each week and patients who showed an appreciable increase in score from week 2 to weeks 3 and 4 were considered suitable for the investigations (Table 1). There were 43 patients in all, 35 of whom were included in the hormone studies and 10 of these and the other eight who were examined daily for follicular growth by ultrasound. The scores for week 4 were greater than for week 3 in all but three of the patients whose scores were marginally higher in week 3. In 26 patients some symptoms, most commonly lethargy, irritability, swollen abdomen and premenstrual abdominal pain, persisted into week 1 of the next cycle with scores of >50: four of these patients had marginally higher scores for week 1 than for week 4. Scores for the second month were similar to those of the first month with medians and ranges of 59(0–224), 2(0–97), 50(0–232) and 162(80–337) for weeks 1, 2, 3 and 4 respectively.

Control subjects for these studies also filled in

Table 1. Symptoms of premenstrual tension (PMT) and total scores in women with PMT and control subjects

Symptoms of PMT recorded on diary cards

Physical. Swollen abdomen, breast pain, swollen fingers, headache, premenstrual abdominal pain.

Psychological: Depression, lethargy, anxiety, aggression, loss of libido, tearfulness, irritability, clumsiness, increased appetite, increased thirst

		Median total scores and ranges in brackets*			
		Week 1	Week 2	Week 3	Week 4
PMT patients:	Hormonal study (*n* = 35)	60 (20–353)	19 (0–157)	85 (0–249)	162 (71–334)
	Ultrasound study (*n* = 18)	52 (0–96)	4 (0–60)	42 (7–218)	138 (65–300)
Controls:	Hormonal study (*n* = 11)	9 (1–50)	4 (0–11)	4 (0–28)	12 (2–32)
	Ultrasound study (*n* = 16)	6 (1–10)	2 (0–11)	3 (0–11)	8 (3–21)

*Each symptom is scored from 0 (no symptoms) to 5 (most severe) diary cards and their total scores were small compared with those of the patients (Table 1). The most common complaints were premenstrual abdominal pain followed by lethargy and headache. The scores tended to be highest in week 1 (five subjects) and in week 4 (four subjects). There were 21 volunteers, 11 acted as controls for the hormonal studies and six of these and the remaining 10 were examined by ultrasound.

Clinical details of the patients and controls are given in Table 2. They were matched as far as possible for age, cycle length and body weight: all subjects were asked to weigh themselves, unclothed, each day first thing in the morning and last thing at night throughout the cycle.

Hormone analysis

Follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, progesterone, cortisol, testosterone, prolactin and thyroid stimulating hormone (TSH) were determined on each blood sample by our routine radioimmunoassays.

The samples from patients were obtained at morning and afternoon clinics between 08.30

Table 2. Clinical details of patients with premenstrual tension (PMT) and control subjects

	PMT patients		Control subjects	
	Hormonal study (n = 35)	Ultrasound study (n = 18)	Hormonal study (n = 11)	Ultrasound study (n = 16)
Age (years)				
mean	35·0	33·3	32·0	29.0
range	(25–44)	(25–44)	(24–41)	(21–41)
Age at menarche (years)				
mean	12·5	13·3	12·5	12·6
range	(10–16)	(11–16)	(10–16)	(11–16)
Length of menstrual cycle (days)				
mean	27·4	26·3	27·9	26·8
range	(21–32)	(23–31)	(25–30)	(24–29)
Body weight (lb)				
mean	136.0	130·0	143.0	132.0
range	(106–187)	(106–160)	(114–174)	(112-166)
Marital status (number):				
Married	29	15	7	14
Single	4	2	4	2
Divorced	2	1	0	0
Parity (number). live births				
0	9	4	5	8
1	5	2	3	4
2	16	11	2	4
3	5	1	1	0
Miscarriages or abortions				
0	21	12	8	12
1	13	5	3	4
2	1	0	0	0
3	1	1	0	0
Methods of contraception				
None	5	4	4	6
IUCD	4	1	2	4
Diaphragm	1	1	1	1
Sterilization	6	2	3	1
Sheath	13	5	1	4
Vasectomy	6	5	0	0

and 17.00 hours. Samples from control volunteers were taken between the same hours except from one subject who could only attend in the evening: her results were omitted from the cortisol analyses to avoid any error related to diurnal variation. The samples were collected at the following times: 21% between 08.30 and 10.30 hours; 30% between 10.30 and 12.30 hours and 49% between 12.30 and 17.00 hours. Results for cortisol and prolactin on all samples collected during these three periods of time were not significantly different. Paired *t*-tests were used to show also that results from the samples taken earliest in the day from each patient did not differ significantly from those taken latest in the day.

The greatest numbers of samples available for hormone analyses were found to have been collected on days 17, 14, 11, 9, 6, 4 and 2 before menstruation and the major analyses were based on these. Other samples were used for a more detailed investigation of the luteal phase and in estimating the day of ovulation.

Statistical analysis

When results were normally distributed statistical assessments were made by analysis of variance or Student's *t*-test. Results were expressed as mean and standard error of the mean (SEM). Wilcoxon ranking tests were used when results were not normally distributed and results were then expressed as medians and ranges.

Ultrasound scanning of follicular growth

This study included 18 of the PMT patients (one scanned for two cycles) and 16 control subjects (four scanned for two cycles). An MK100 sector scanner was used to measure the follicular diameters using a full bladder technique. The diameters were recorded daily until the maximum diameter was attained before the rupture of the follicles. Oestradiol was also measured on serum samples taken at the same time.

Results

Serum concentrations of the gonadal steroids in 35 PMT patients and 11 control subjects are shown in Fig. 1. The peak concentrations of progesterone in the luteal phase were similar in the two groups, but in the early luteal phase progesterone tended to rise earlier in the patients than in the controls, and over days 14, 11 and 9 before menstruation, the concentrations were significantly higher in the patients with PMT ($P<0{\cdot}05$). At the end of the cycle the concentrations in the patients fell slightly earlier than in the controls and on days 4 and 2 before menstruation the concentrations were significantly lower than in the controls ($P<0{\cdot}05$).

The oestradiol patterns were similar in the two groups except on days 17 and 14 before menstruation. The maximum concentrations in the patients occurred on day 17 and in the controls on day 14 and analysis of variance showed that the differences were significant ($P<0{\cdot}001$).

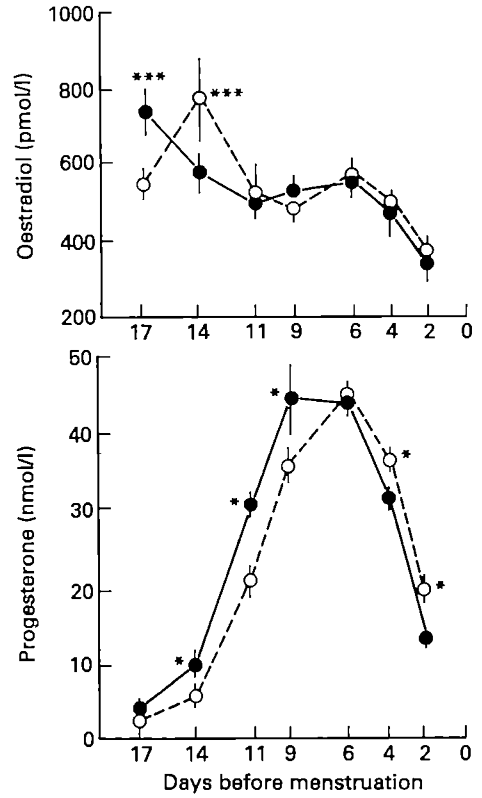

Fig. 1. Serum concentrations of oestradiol and progesterone in 35 women with PMT (●——●) and in 11 control subjects (12 cycles) (○---○) during the last 17 days of the cycle Results are expressed as means ±SEM. Significance of differences between results of PMT patients and control subjects: *$P<0{\cdot}05$; ***$P<0{\cdot}001$

These steroid patterns could be explained by supposing that some of the PMT patients had ovulated earlier in the cycle than the controls. Although the study had not been specially designed to identify the day of ovulation, it was clear from the results available that the LH and FSH surges occurred 14 days or less before menstruation in 17 patients (LH range 14–117 units/l) and nine controls (LH 10–83 units/l) (group A) and more than 14 days before menstruation in the other 18 patients (LH 12–107 units/1) but in only two controls (LH 16–50 units/l) (group B).

When the gonadal steroid results were calculated according to this classification (Table 3), the mean concentrations of oestradiol were significantly greater in group B patients than in group A patients ($P<0{\cdot}01$) or in controls ($P<0{\cdot}05$) on day 17 before menstruation and were significantly less in group B patients on day 14 than in the other two groups ($P<0{\cdot}01$). The earlier rise in progesterone in group B patients resulted in higher concentrations on days 14–11 before menstruation compared with those in group A patients ($P<0{\cdot}01$) and on days 11 and 9 compared with those in group A controls ($P<0{\cdot}01$). Later in the cycle oestradiol concentrations did not differ between the groups but progesterone levels in group B patients at 4 days ($P<0{\cdot}05$) and 2 days ($P<0{\cdot}01$) before menstruation were lower than in group A controls.

In the last 6 days of the cycle LH levels did not differ significantly between group A and group B patients but both groups had higher LH concentrations than the control subjects on days 6 and 2 before menstruation (Table 4). FSH concentrations in the various groups were not significantly different on these days.

The luteal phase was now examined by considering the LH ovulatory surge as day 0. Fig. 2

Table 3. Gonadal steroid concentrations in groups A and B of patients with premenstrual tension (PMT) and control subjects

	Days before menstruation						
	17	14	11	9	6	4	2
Oestradiol (pmol/l)							
Patients with PMT							
Group A ($n=17$)	526	753†	520	542	600	541	364
	(53·6)	(84·9)	(59·2)	(51·0)	(66·0)	(86·3)	(77·0)
Group B ($n=18$)	844†	426	485	541	576	454	291
	(85·0)	(51·7)	(35·9)	(37·8)	(25·2)	(27·9)	(25·0)
Control subjects							
Group A ($n=9$)	562*	904**	534	421	592	561	392
	(50·9)	(111·7)	(88·9)	(18·7)	(58·9)	(38·3)	(40·2)
Group B							
Subject 1	650	550	505	540	550	400	180
Subject 2	550	280	510	550	495	460	310
Progesterone							
Patients with PMT							
Group A ($n=17$)	2·1	4·8	21·1	41·5	41·9	34·6	16·5
	(0·3)	(1·1)	(3·4)	(4·9)	(3·5)	(4·0)	(2·5)
Group B ($n=18$)	2·8	15·0†	38·8†	46·8	50·2	28·8	9·5
	(0·4)	(3·7)	(3·7)	(3·6)	(2·6)	(1·7)	(1·5)
Control subjects							
Group A ($n=9$)	2·5	5·6	18·4**	31·6**	47·9	38·9*	21·2**
	(0·8)	(1·7)	(4·0)	(4·0)	(3·4)	(4·2)	(4·1)
Group B							
Subject 1	1	2	42	64	58	31	7
Subject 2	1	13	34	54	28	25	13

Significance of differences between group A and group B PMT patients: † $P<0{\cdot}01$.
Significance of differences between group B PMT patients and group A controls: *$P<0{\cdot}05$, **$P<0{\cdot}01$.
Results are means (SEM).

shows that the progesterone concentrations in the PMT patients and the controls were almost identical for the first 7 days of the luteal phase, but during the last 7 days of the cycle the concentration in group B patients was significantly higher than in the other groups ($P<0{\cdot}001$). The oestradiol pattern was similar throughout the cycles irrespective of whether the patients were in group A or in group B.

Cortisol

Concentrations of cortisol in both groups were fairly constant throughout the 17 days before menstruation and there was no obvious cyclical effect. The mean results were uniformly higher in patients (range of means 301–334 nmol/l) compared with controls (range of means 199–266 nmol/l) although all results were within the accepted normal range. Analysis of variance on all results indicated that the concentrations in the PMT patients were significantly higher ($P<0{\cdot}001$) than in the controls the overall means being 324 nmol/l in the patients and 236 nmol/l in the controls.

When the results from PMT patients of groups A (mean 319 nmol/l) and B (mean 329 nmol/l) were analysed separately, no significant differences were found between them.

Table 4. Luteinizing hormone (LH) concentrations on days 6 and 2 before menstruation in groups A and B of patients with premenstrual tension (PMT) and control subjects

Study group	Luteinizing hormone (units/l)	
	Day 6	Day 2
Patients with PMT		
Group A (n=17)	6·0 (0·9)*	5·3 (0·7)*
Group B (n=18)	5·3 (0·6)**	6·4 (0·6)**
Control subjects		
Group A (n=9)	2·8 (0 5)	3·3 (0·4)

Results are means (SEM)
*$P<0{\cdot}05$. PMT *vs* controls, **$P<0{\cdot}01$: PMT *vs* controls

Prolactin

Mean concentrations over the last 17 days of the cycle ranged from 288 to 418 units/l in the control subjects and from 343 to 396 units/l in the PMT patients These concentrations were not significantly different and the overall averages were 336 units/l in controls and 371 units/l in the patients. The levels in patients in group A and

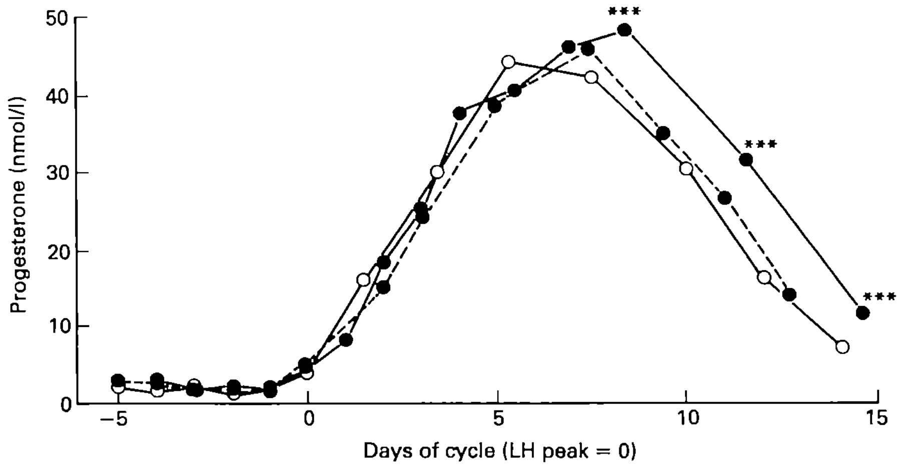

Fig. 2. Serum concentrations of progesterone in 18 patients with PMT, group A (●——●), 17 with PMT, group B (●– – –●) and in nine control subjects (○——○) adjusted to the LH peak (day 0). Significance of differences between results of PMT group B patients and control subjects: ***$P<0{\cdot}001$.

group B did not differ, group A averaging 391 units/l and group B 356 units/l.

Testosterone and TSH

There were no significant differences between the groups in either testosterone or TSH concentrations throughout the last 17 days of the cycle.

Ultrasound scanning of follicular growth

The mean follicular diameters in the late follicular phase in 18 patients (19 cycles) with PMT and 16 control subjects (20 cycles) indicated that the rates of growth were similar in the two groups (Fig. 3). However, the mean diameters on each of the 5 days leading to maximum growth were smaller in the patients than in the controls (differences significant by analysis of variance at $P<0{\cdot}01$). The mean diameter at ovulation, however, was within the documented normal range for follicular diameters at ovulation. This finding held irrespective of whether the patients were group A or group B. Oestradiol concentrations on the same days were also lower on each occasion in the patients and the differences from controls and the correlation with follicular diameter were highly significant ($P<0{\cdot}001$).

The total lengths of the cycles did not differ significantly but the luteal phases ranged from 12 to 15 days in the controls and from 10 to 19 days in the patients. Only 2 of the 20 control luteal phases were longer than 14 days, whereas nine of the 19 luteal phases from patients lasted between 15 to 19 days.

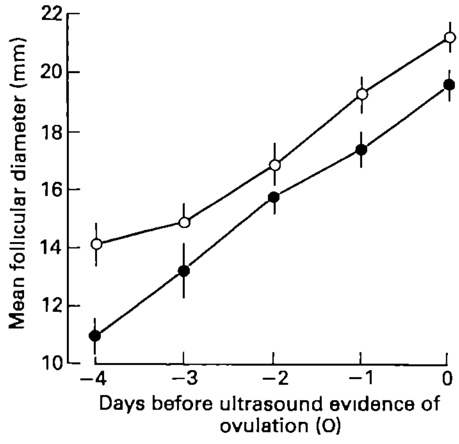

Fig. 3. Mean follicular diameters (with SEM) in 16 control subjects (○——○· 20 cycles) and 18 PMT patients (●——●. 19 cycles) related to the day of ovulation as judged by ultrasound scanning.

Weight changes

The median changes in weight in control subjects and groups A and B patients from morning to evening were least in the control subjects and greatest in group B patients (Table 5), both in the late follicular (the last 7 days before ovulation) and luteal phases (last 7 days of cycle). In each group of subjects the change was slightly greater in the luteal phase and examination of the changes both AM and PM showed that they were again greatest in group B patients and least in the controls, the differences being highly significant.

Discussion

Reported studies on oestrogen and progesterone concentrations in women with PMT are conflicting. In accordance with the present findings O'Brien *et al.* (1980) noted elevated levels of progesterone in patients in the early luteal phase, while the reduced levels found at the end of the cycle in the present study are in agreement with results reported by Bäckstrom *et al.* (1976). The pattern of progesterone levels, however, was not found to be constant in the present group of patients and the explanation appeared to be that some patients ovulated slightly earlier than others. The various indices of ovulation were used to demonstrate that there were two groups of patients, group A who ovulated not more than 14 days before menstruation and group B who ovulated before this time. The proportion of patients ovulating early (18 out of 35) was higher than in the control group where there were only two out of 11. The cycle lengths were not significantly different between the patients and the controls so those ovulating earlier must have had slightly longer luteal phases and this was demonstrated by the results of ultrasound scanning of the follicles. There was no apparent abnormality in steroid production during the early luteal phase, however, since when the results were referred to the day of the LH surge as day 0, the progesterone con-

Table 5. Weight changes from morning to evening, and from the follicular to the luteal phase in patients with premenstrual tension (PMT) in groups A and B and in control subjects

	Change in weight (lbs)			
	Morning to evening		Late follicular to late luteal phase	
	Late follicular	Late luteal	Morning	Evening
Control subjects	0·707	0·933	−0·277	−0·051
(*n*=10)	(−0·07—2·15)	(0·21—1·71)	(−3·72—1·72)	(−3·43—1·71)
Patients with PMT				
group A	0·86	0·97	0·425	0·457
(*n*=17)	(0—2·71)	(0—2·86)	(−2·14—2·71)	(−2·71—2·71)
group B	1·00	1·20	1·465***	1·514**
(*n*=18)	(0—2·42)	(0—2·43)	(−0·29—2·86)	(0·57—4·29)

The increases in weight in the luteal phase from the weight in the follicular phase in group B patients was significantly greater than in controls ***$P<0·001$, **$P<0·01$

centrations were similar in all groups. In group B patients, however, the luteal phases, being slightly longer, had higher progesterone concentrations than those in group A or in control patients over the last 7 days.

Ultrasound scanning of the growing follicles indicated that on average the follicular diameter on the days before ovulation was significantly lower in the PMT patients than in the controls. Oestradiol concentrations on these days were also significantly lower. These findings suggested that the rupture of the follicles following the release of LH is premature and appeared to occur even in those patients in group A whose LH surge and other hormonal changes indicated that ovulation did not occur more than 14 days before menstruation.

Significant weight changes have not been reported in women with PMT (Andersch *et al.* 1979; O'Brien *et al.* 1979), although they have been suspected to occur to account for the common symptoms of bloatedness and peripheral oedema. The changes noted here were relatively small but they were significantly greater in group B patients than in group A or in controls. The mechanism underlying these findings is not clear from the present results. The changes are not comparable with the large diurnal variations which occur in the fluid retention syndrome (Dunnigan 1983). Investigations reported elsewhere on aldosterone levels (O'Brien *et al.* 1979; Munday *et al.* 1981) and on the renin–angiotensin system (O'Brien *et al.* 1979) have not revealed any gross abnormalities and it has been considered that the symptoms may be related to a redistribution of fluid rather than to an increase in total body fluid.

Patients with severe symptoms are likely to be stressed and therefore a raised cortisol level in the luteal phase would not be unexpected. The present study not only demonstrated this but showed that the level is raised before the time in the cycle that the symptoms are most severe. Prolactin, also affected by stress, however, did not show any abnormality.

The relationship, if any, between hormonal abnormalities and symptoms in women with PMT is therefore no clearer. It has been proposed that there may be an underlying abnormality of endogenous opiates or related compounds (Halbreich & Endicott 1981; Reid & Yen 1981). This could certainly help to explain the depression, lowered pain threshold etc. in these patients. A lack of β-endorphin or enkephalins would also help to explain some of the present findings. These peptides have been shown to affect the release of LH and of prolactin in certain conditions. The antiopiate, naloxone, in high doses releases LH, whereas enkephalin analogues and endorphin suppress LH. An underlying deficiency of such a compound would offer an explanation for the premature release of LH at ovulation and for the significantly higher levels of LH in the last week of the luteal phase indicated by the recent studies. If there is a defect it must be assumed to begin before the symptoms arise and that other factors produced during the luteal phase augment the effect of the lack of endogenous opiate. Whether the raised cortisol levels are also related in view of the fact that the prohormone for ACTH is also the prohormone for β-endorphin, cannot be adequately answered from the present study.

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Long-term effects of the menopause and sex hormones on skin thickness

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Summary. Skin collagen content and skin thickness in a group of postmenopausal women who had been treated with sex hormone implants were compared with those in an untreated group of similar women. Both skin collagen content and thickness were found to be significantly greater in the treated than in the untreated group. In the untreated women skin collagen content declined in relation to menopausal age but not to chronological age. No correlation was found with menopausal age, chronological age or duration of therapy in the treated group. These data suggest that skin collagen is influenced by the sex hormone status and declines after the menopause, contributing to the increase in urinary hydroxyproline excretion that has been reported to occur at this time.

Albright *et al.* (1940) first postulated that loss of oestrogens leads to bone loss after the menopause, but the effects of oestrogen deficiency on the skin collagen content and skin thickness have not been reported Although it has been suggested that there is a link between the quality of the skin and bone mass, (McConkey *et al* 1969; Gordon 1977), the possible effect of sex hormones on skin has not been adequately investigated. Brincat *et al.* (1983), in a study comparing 29 postmenopausal women with 26 women of similar age, who had been on sex hormone replacement for between 2 and 10 years, showed that the treated group had a higher skin collagen content than the untreated group, thus suggesting that sex hormones have a direct effect on the skin. Shuster *et al.* (1970) suggested that it is an increase in androgen levels that gives hirsute women their higher skin collagen and skin thickness

In order to investigate the effects of sex hormones on the skin, we have studied the skin collagen content and the skin thickness in a large number of women treated with sex hormones and in untreated women at various stages after the menopause.

Patients and methods

The skin collagen content was measured in 52 postmenopausal women, who had been treated with oestradiol and testosterone implants for 2 to 10 years, and compared with that in a group of 66 postmenopausal women who had never received sex hormone therapy.

The two groups were similar in age, the mean age was 50·5 years in the treated group and 50·3 years in the untreated group. The treated group of women were maintained on implants of 50 mg of oestradiol (E_{50}) and 100 mg of testosterone (T_{100}) (Brincat *et al.* 1984) administered every 6 months. Those women who had a uterus were given 5 mg of norethisterone for 7 days to produce a regular bleed and to prevent endometrial hyperplasia (Thom *et al* 1979) The mean duration of therapy in the treated group was 5·2 years. The mean number of years since the menopause was 8·8 in the treated group and 8·1 in the untreated group. In patients who had had a surgical menopause, menopausal age was calculated as the number of years since oophorectomy.

Skin thickness was measured in 30 of the treated group compared with that in 33 of the untreated group.

The skin collagen content of the 66 and an additional 11 untreated women was correlated with chronological age and also with menopausal age (years since the menopause, range 0·25–20). In the 52 treated women skin collagen content was correlated with chronological and menopausal age and with the duration of therapy. Again both groups were of similar age.

Skin collagen content

Punch biopsy specimens of the skin, 3 mm in diameter, were taken from the right thigh 5 cm below the greater trochanter. The hydroxyproline content was determined as described by Woessner (1961) and the collagen content was calculated as described by Neuman & Logan (1950). The result was expressed in μg/mm². This is the most satisfactory way of expressing the skin collagen content (Shuster & Bottoms 1963).

Skin thickness

The forearm skin thickness was measured using a modification of the X-ray technique described by Black (1975) (Fig. 1). A wooden block compresses the skin gently and enables the two parallel lines corresponding to the top of the epidermis and the bottom of the dermis to be identified easily. The skin thickness is then measured using needle-pointed vernier calipers.

Spearman's rank-order correlation (ρ) was used in the calculation of all correlations. The significance levels were calculated using the Wilcoxon rank test. The results were analysed by the King's College Hospital Medical School Computer Unit, using the Statistical Package for Social Sciences (SPSS).

Results

A highly significant correlation ($\rho = 0{\cdot}52$, $P < 0{\cdot}0001$, $n = 63$) was found between the radiological assessment of forearm skin thickness and thigh skin collagen.

There was a highly significant correlation between thigh skin collagen content and menopausal age in the untreated patients ($\rho = 0{\cdot}38$, $P < 0{\cdot}001$) but there was no such correlation with chronological age. Fig. 2 shows that the mean collagen content declines exponentially after 2 to 4 years menopausal age. No fall in collagen content was recorded in the treated group (Fig. 2). There are no values available for less than 2 years postmenopausal age in the treated group since all the women had been treated for at least 2 years. There was no correlation between skin collagen and duration of treatment.

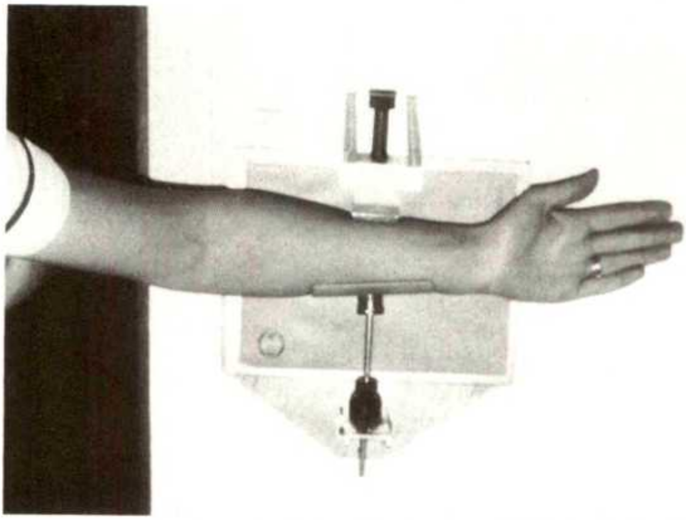

Fig. 1. Technique for X-raying the skin of the forearm. A wooden block on the radial side gently compresses the skin and the X-raying plate is placed behind the forearm.

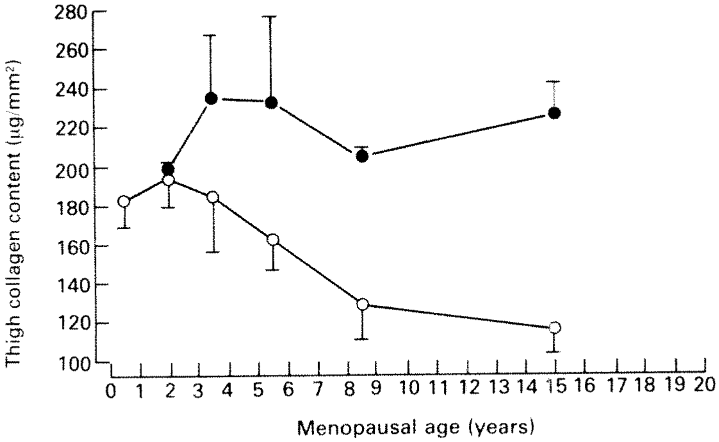

Fig. 2. Relation between thigh skin collagen content and menopausal age in 52 patients treated with sex hormone implants (●) and in 77 untreated patients (○).

The mean skin collagen content was 164·8 (SEM 8·4) μg/mm² in the untreated patients and 34% greater, 221·12 (12·1) μg/mm² ($P<0.001$), in the 52 patients receiving hormone replacement. The mean skin thickness in the 30 treated women was 1·19 (SEM 0·02) mm being 30% thicker ($P<0.001$) than that in the 33 untreated women (mean 0·93, SEM 0·03 mm).

Discussion

We have demonstrated that skin thickness, measured radiologically, is a good reflection of the skin collagen content, and is a cheap, non-invasive and more convenient method of assessing skin collagen than skin biopsies.

We present evidence of an inverse relation between skin collagen content and years since the menopause, independent of the actual age of the patient. This suggests that the decline in skin collagen is due to the loss of ovarian oestrogens. That effect is lost in the treated group of women indicating that treatment with sex hormones prevents or reverses the loss of skin collagen after the menopause. The lack of correlation between skin collagen content and duration of treatment suggests that the skin collagen content stabilizes after a period of sex hormone treatment which is probably <2 years.

Our results suggest that skin contributes to the increased urinary hydroxyproline excretion seen in postmenopausal women. Similarly the decline in hydroxyproline excretion that occurs with oestrogen therapy may be due in part to the effects of oestrogen on postmenopausal skin.

Gallagher & Nordin (1973) attributed the increase in urinary hydroxyproline excretion after the menopause to an increase in bone resorption. Crilly *et al.* (1980) reported a similar rise that was completely reversed with oestrogen therapy which he attributed to a decrease in bone resorption.

Half the body's collagen is in the skeleton with most of the remainder in the skin (Forbes *et al.* 1956). Although urinary hydroxyproline gives an indication of collagen turnover, it does not provide an accurate measure of collagen degradation since, because of renal reabsorption, urinary hydroxyproline is a variable fraction of the hydroxyproline that is released during collagen breakdown (Kivviriko 1970; Florkin 1980). An estimate of the amount of skin collagen breakdown after the menopause can be calculated. The average weight of the women attending our clinic is 66·2 kg and the average height 1·67 m. The average surface area is therefore 1·8 m² (Davidson *et al.* 1979). The mean skin collagen content at 3 months after menopause is 183·11 μg/mm² and at 9 years is 129·6 μg/mm², a difference of 53·51 μg/mm². Assuming a uniform rate of loss of collagen from the skin, a daily collagen loss of 29·3 mg occurs. Since collagen contains large amounts of hydroxyproline (Neuman & Logan 1950) this collagen breakdown would be reflected in an increase in urinary excretion of hydroxyproline.

Because of the exponential nature of the curve (Fig. 2), the figure for collagen loss that has been calculated is probably too high in the initial 2 to 4 postmenopausal years, and possibly too low for the subsequent years when the skin collagen content is declining more sharply.

In conclusion, it appears that the postmenopausal increase in urinary hydroxyproline is not derived entirely from bone collagen, and there is probably a major contribution from the skin. This implies that increased bone resorption may not be as important a feature as has been suggested and supports the role of decreased collagen formation by osteoblasts in the development of postmenopausal bone loss.

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The effects of age and body composition on circulating serum oestrogens and androstenedione after the menopause

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Summary. Circulating levels of oestrone, oestradiol and androstenedione were measured in two large groups of postmenopausal women, in one group the women were between 46 and 56 years of age and in the second, older group they were 70 years of age. In addition the fat mass was calculated from the height, weight and age of the women. Serum concentrations of both oestrogens did not change with age, whereas the serum androstenedione concentration decreased significantly. A change in body composition included decreased height and increased fat mass in the older group. Serum concentrations of both oestrogens correlated significantly with the fat mass and serum androstenedione as well as with each other. From the correlation analysis it may be concluded that the conversion rate of androstenedione to oestrone, and of oestrone to oestradiol, increases with age, which presumably explains the unchanged concentrations of the circulating oestrogens in relation to postmenopausal age, although the precursor decreases during the same period.

The production rates of oestradiol (E_2) and oestrone (E_1) at the menopause drop to less than 10% and 33%, respectively, of the premenopausal rates (Soules & Bremner 1982). Opinions differ as to whether the low levels of both oestrogens change throughout postmenopausal life (Marshall *et al.* 1977*a*; Meldrum *et al.* 1981; Badawy *et al.* 1979).

Serum oestrone is the major oestrogen in the postmenopausal woman. Its principle source is the peripheral conversion of androstenedione (Soules & Bremner 1982; Grodin *et al.* 1973). The origin of androstenedione is the adrenal glands, although a minor production seems to take place in the ovaries (Soules & Bremner 1982). The circulating level of androstenedione is approximately 50% of that before the menopause (Soules & Bremner 1982), but there is some controversy as to whether this concentration remains constant (Meldrum *et al.* 1981) or declines (Crilly *et al.* 1979; Hummer *et al.* 1983) as a function of menopausal age. Serum oestradiol derives mainly from peripherally converted oestrone, but a minute production occurs in the ovaries (Soules & Bremner 1982). A number of methods to determine the serum concentrations of oestrogens have been described (Grodin *et al.* 1973; Marshall *et al.* 1977*b*). How-However, the sensitivity is essential in the reliable measurement of the reduced serum levels of oestrogens, especially oestradiol in postmenopausal women. Varying sensitivity and specificity of these methods probably explain some of the discrepancies in the literature concerning the interrelations of oestrone, oestradiol and androstenedione.

The aim of the present study was to clarify the age-related changes and interrelations of oestrone, oestradiol and androstenedione in postmenopausal women, using specific and sensitive radioimmunoassays.

Methods

Two groups of postmenopausal women participated in the study.

Group 1 included 144 healthy volunteers, aged 46–56 years (mean 52·4, SD 2·3 years) who were selected by questionnaire and medical screening examination. They had passed their natural menopause 2½ to 5 years before the study, and were free of past or present diseases known to influence the variables studied. Further details concerning the selection are given elsewhere (Christiansen *et al.* 1980).

Group 2 included 147 women, 70 years of age, who were selected from nine suburban districts with a population composition representative of the Danish population. Further details concerning the selection of these women are given elsewhere (Jensen *et al.* 1982).

All blood samples were taken in the morning after an overnight fast and tobacco abstinence. The serum samples were stored at −20°C until assayed. The serum concentrations of oestrone and oestradiol were determined in all participants. Androstenedione was determined in all participants in group 2 and in a subpopulation of 66 women in group 1 (see below).

Informed consent was obtained from each participant according to the Helsinki Declaration II, and both trials were approved by the ethical committees of the participating institutions.

E_2 radioimmunoassay

Antisera, ^{125}I-labelled oestradiol, assay buffer and standard oestradiol were supplied by CIS International, France (Ref. ESTRK-125). Diethylether (art. 6050) was from E. Merck, Darmstadt, W. Germany. Glass tubes (12 × 75 mm) were used for all assay steps.

Serum (300µl) was extracted by shaking vigorously on a Multitube vortexer for 20 min with 3 ml diethylether. After phase separation by centrifugation at 4°C and 2000 *g* for 5 min, the aqueous phase was frozen in a dry ice/acetone mixture. The entire organic phase was decanted into another assay tube and evaporated to dryness at 30°C under nitrogen. The residue was dissolved in 300 µl assay buffer and incubated overnight at room temperature with 100 µl of the ^{125}I-labelled oestradiol solution and 100 µl antiserum dilution. Tubes containing 300 µl of standard oestradiol covering a range of 0·5 pg to 50 pg per assay tube were similarly incubated overnight with tracer and antiserum. To separate the free and bound fraction 1 ml of the second antibody, which was precipitated in a low-concentration polyethylene glycol solution, was added. After incubation at room temperature for 15 min, the tubes were centrifuged at 4°C and 3000 *g* for 15 min. The supernatant was discarded and the radioactivity in the precipitate was measured in a gamma-scintillation counter

The maximum binding and the non-specific binding of tracer were 61·1±6·8% and 4·9±5·1%, respectively ($n = 13$). The detection limit was 6 pmol/l, when assaying 300 µl serum. The intra- and inter-assay variations determined in low control samples were 8·8% (25 duplicate determinations) and 14% ($n = 23$), respectively. Blank values obtained by extraction of 300 µl saline were not significantly different from zero dose. The accuracy was assessed by addition of unlabelled oestradiol to a serum sample with a concentration of 120 pmol/l in doses corresponding to 30, 60, 110, and 230 pmol/l. The mean recovery of duplicate measurements was 107·6%, range 101–114%.

E_1 radioimmunoassay

Antiserum was generated in rabbits in response to an oestrone-6-oxime-protein preparation from Wien Laboratories Inc., New Jersey, USA, lot no. 03303, one ampoule diluted with 10·4 ml assay buffer (2080 tubes). Oestrone for standards was from Sigma, Missouri, USA and dissolved in ethanol, 100 mg/l. Assay buffer was 0·01 mol/l phosphate (pH 7·4) containing 0·01 mol/l EDTA, 0·1% (w/v) sodium chloride and 0·1% (w/v) gelatin. Scintillation liquid was Aqua Luma Plus from Lumac Systems AG, Basel, Switzerland. Diethylether (art. 6050) and methanol (art. 6009) were from E. Merck, Darmstadt, W Germany. Activated charcoal was Norit A, Serva, Heidelberg, W. Germany, and Dextran T-80 supplied by Sigma, Missouri, USA, oestrone (2,4,6,7–^{3}H(n)) with specific activity 80–115 Ci/mmol was from New England Nuclear, Boston, USA

A 1000-µl serum sample was extracted with 3 ml diethylether according to the procedure as described for oestradiol. The dry residue was dissolved in 1000 µl assay buffer and incubated at 0°C (water–ice bath) with 7 nCi (5 pg) ^{3}H-E_1/50 µl assay buffer and 50 µl antiserum The antibody-bound fraction was separated from the free oestrone by addition of 500 µl charcoal solution (2·4% Norit A, 0·24% Dextran T-80 in assay buffer without gelatin) and further incubated at 0°C for 5 min. The tubes were centrifuged at 4°C and 3000 *g* for 15 min. A 300-µl sample of the supernatant was added to 5 ml scintillation liquid and the radioactivity measured in a Beckman LS 7000 liquid scintillation counter. The maximum binding and non-specific binding of the tracer were 77·2±4% and 3·0±16%, respectively ($n = 12$). The detection limit was 44 pmol/l when assaying 1 ml serum. The intra- and inter-assay variations were 5·6% (20 duplicate determinations) and 10·8% ($n = 23$), respectively. Blank values obtained by extraction of 1000 µl saline were not significantly different from zero dose. The accuracy was assessed by addition of unlabelled oestrone to a serum sample with a concentration of 148 pmol/l in doses corresponding to 10, 20, 30, 40, 80 and 100 nmol/l. The mean recovery of duplicate determinations was 98·2%, range 94–102%

Androstenedione radioimmunoassay

The assay procedure, which has been described in details (Hummer *et al* 1983), resulted in an intra- and inter-assay variation of 7% and 11%, respectively. The detection limit of the assay was 0·2 nmol/l, when assaying 1 ml serum

Body height and weight These were measured with participants wearing indoor clothes, but without shoes

Fat mass This was calculated using the formula of Boddy *et al* (1972),

(1) Lean body mass (LBM) (kg) =
$18{\cdot}23 + 1{\cdot}014 \times 10^{-2}$ (14·76 × weight (kg) + 22·07 × height (cm) − (9·05 × age (years) − 1669).

(2) Fat mass (kg) =
body weight (kg) − LBM (kg)

Statistical analysis

Student's *t*-test for unpaired data and linear regression analysis were used.

Results

Table 1 gives the clinical data on gross morphology in the two populations The mean body weight in the two groups was virtually similar, whereas the height in group 2 was highly significantly lower than in group 1 ($P<0{\cdot}001$). Correspondingly, the fat mass in the older women was significantly higher ($P<0{\cdot}001$). The serum concentrations of both oestrogens were similar in the two groups but the mean serum androstenedione concentration was significantly lower in the older population ($P<0{\cdot}001$) (Table 1).

The coefficient of correlations from the linear regression analysis between the serum concentrations of the three hormones and the calculated fat mass are given in Table 2. The *r* values for oestrone versus androstenedione and oestradiol versus oestrone were significant in both groups, as were the *r* values of oestradiol versus fat mass. In contrast, the relation of oestrone and fat mass appeared to be weak in the

Table 1. Clinical data on height, weight, calculated fat mass and serum concentrations of oestrone (E_1), oestradiol (E_2) and androstenedione (A) in two groups of postmenopausal women

	Early postmenopausal women ($n = 144$)	Elderly postmenopausal women ($n = 147$)	Significance of difference
Body weight (kg)	63·6 (11·9)	64·2 (9·7)	NS
Height (cm)	162·1 (5·7)	157·4 (5·1)	$P<0{\cdot}001$
Calculated fat mass (kg)	21·3 (9·6)	24·5 (8·0)	$P<0{\cdot}001$
Serum E_1 (pmol/l)	169 (52)	164 (53)	NS
Serum E_2 (pmol/l)	15 (9)	15 (9)	NS
Serum A (nmol/l)	2·8 (1·0)*	2·0 (0·9)	$P<0{\cdot}001$

* $n =$ 66 (see text).
Results are shown as means (SD).

Table 2. Correlations between serum oestrone (E_1), oestradiol (E_2), androstenedione (A) and fat mass in two groups of postmenopausal women

Correlations between	*n*	Early postmenopausal women	*n*	Elderly postmenopausal women
E_1/A	66	$r = 0{\cdot}397$***	147	$r = 0{\cdot}513$***
E_2/E_1	144	$r = 0{\cdot}211$**	147	$r = 0{\cdot}352$***
E_2/fat mass	144	$r = 0{\cdot}310$***	147	$r = 0{\cdot}296$***
E_1/fat mass	144	$r = 0{\cdot}183$*	147	$r = 0{\cdot}140$ NS
E_2/A	66	$r = 0{\cdot}078$ NS	147	$r = 0{\cdot}215$**

*$P<0{\cdot}05$; **$P<0{\cdot}01$; ***$P<0{\cdot}001$; NS, not significant.

early postmenopausal women and was absent in the older postmenopausal group. A significant relation between serum oestradiol and androstenedione could not be demonstrated in the early postmenopausal women, but was significant in the older women ($P<0{\cdot}01$). A comparison of the regression lines obtained from serum oestrone versus androstenedione and oestradiol versus oestrone in the two populations revealed similar intercepts, whereas the slope in the older group was 50% higher than that obtained in the younger postmenopausal group (Fig. 1).

Discussion

There is substantial evidence that oestrogens play a crucial, if not a causative, role in the development of postmenopausal osteoporosis (Christiansen *et al.* 1980; Lindsay *et al.* 1976). Moreover, since osteoporosis is more common in the slender postmenopausal woman (Dalén *et*

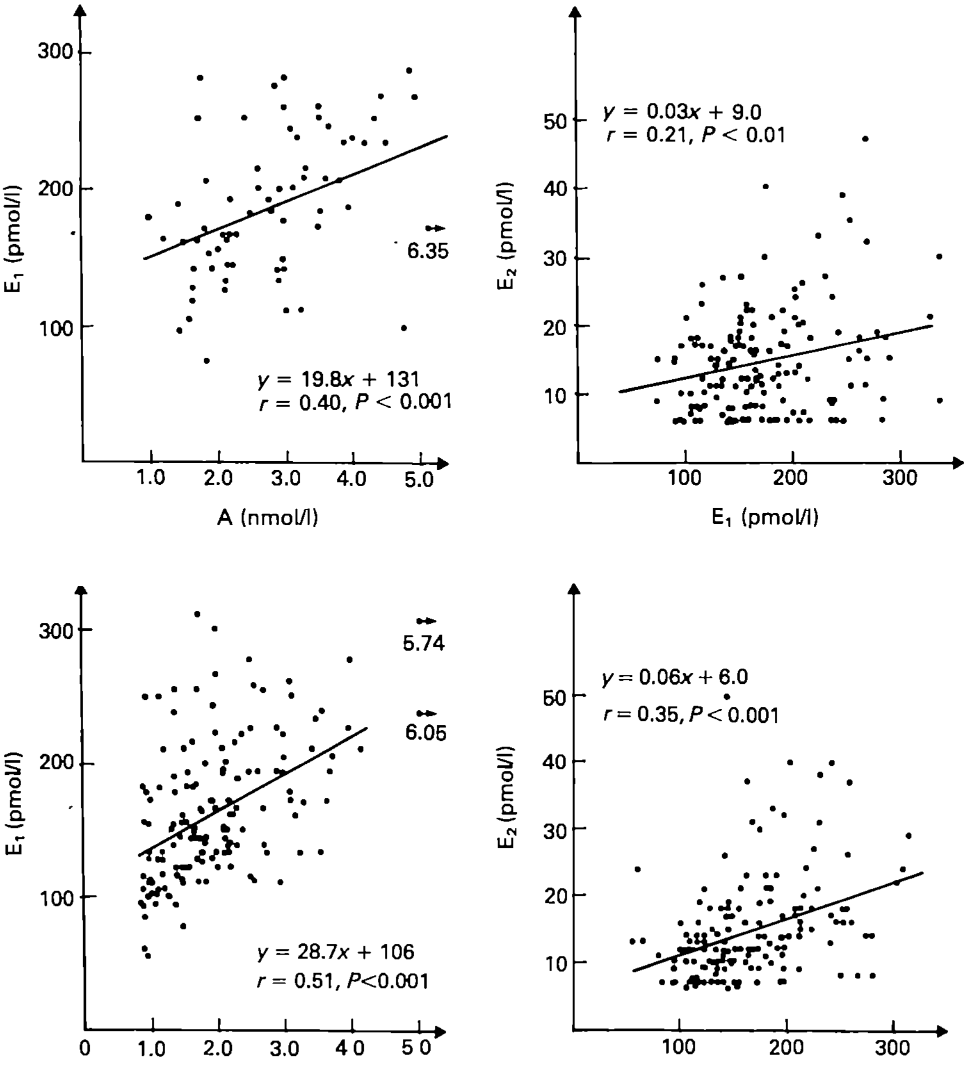

Fig. 1. Inter-relations oestrone (E_1), oestradiol (E_2) and androstenedione (A) in early (top) and elderly (bottom) postmenopausal women.

al. 1975; Daniell 1976), a positive relation between the serum oestrogens and fat mass would be expected. Indeed, such a relation was recently demonstrated in studies comprising relatively few patients (Badawy *et al.* 1979; Poortman *et al.* 1981). The present study clearly supports these findings, but the relation between serum oestradiol and fat mass appeared to be stronger than between oestrone and fat mass. This might be explained by a higher metabolic clearance rate of oestrone than of oestradiol (Soules & Bremner 1982).

Our data confirm the importance of androstenedione as a precursor of oestrone in both groups of postmenopausal women (Table 2). The absent correlation between serum oestradiol and androstenedione in the early postmenopausal group indicates that there is a residual ovarian secretion of oestradiol in the young postmenopausal women which is lost in advanced postmenopausal life (Marshall *et al.* 1977*a*; Soules & Bremner 1982).

Extension of the regression lines in the correlations of serum oestrone and androstenedione results in intercepts on the oestrone axis at about 100 pmol/l which is in accordance with the findings of Marshall *et al.* (1977*a*). This denotes a higher oestrone/androstenedione ratio (which presumably reflects the conversion rate of androstenedione to oestrone) at lower levels of androstenedione and this might explain the fact that, although serum androstenedione decreases as a function of age, serum concentrations of both oestrogens remain unchanged. Moreover, the similarity of the mean serum oestradiol concentrations in the two postmenopausal populations indicates that the termination of the ovarian production of oestradiol in the older women may be compensated by a higher conversion rate of oestrone to oestradiol with age. The difference between the slopes in the relation of oestradiol and oestrone in the younger and older postmenopausal women, respectively, support this hypothesis.

The present study demonstrates a decrease in circulating concentrations of androstenedione as a function of postmenopausal age, whereas the serum oestrogens remain constant throughout this period. Body fat was found to be related to both oestrogens. Thus, the effect of body composition, rather than the biological age, on the circulating concentrations of oestrogens seems to be a significant factor in a variety of end-organ effects of oestrogen depletion in postmenopausal women, including the development of manifest postmenopausal osteoporosis.

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Training in tubal microsurgery

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Summary. The restoration of normal tubo-ovarian function was investigated in a training programme using oviduct anastomosis in the rabbit as an experimental model. Ovulation rate, pregnancy rate, nidation index, implantation failure index and degree of adhesions were used as parameters. More than 100 anastomoses had to be performed to reach a perfect degree of atraumatic, function-restoring surgery. It is concluded that the most difficult aspect in female infertility surgery is not the use of the operating microscope but the experience in applying the principles of atraumatic surgery.

Several authors such as Paterson & Wood (1974), Winston & McLure Browne (1974), Winston (1975), Paterson (1978) and Eddy *et al.* (1980) have shown in experimental conditions that microsurgical techniques are superior to conventional techniques in restoring tubo-ovarian function and preventing adhesion formation. However, the operating microscope is not a magic tool and the skill of atraumatic surgery must be gained through practice. In the present study we investigated the degree of training in microsurgical technique needed to acquire the expertise for the restoration and preservation of normal tubo-ovarian function after oviduct section and anastomosis in rabbits.

Material and methods

Training model

Tubal section and anastomosis in female New Zealand white rabbits weighing 3000–4000 g was used as the training model. Tubo-ovarian function was investigated in five stages during the period of training and each stage involved 15 animals (groups 1–5). All anastomoses were performed by one surgeon.

The animals were housed with a 14 h light/10 h dark regimen and received a daily pellet diet of 115 g and unlimited water. The animals were starved 12 h before the operation. After intramuscular induction of anaesthesia with Hypnorm (0·4 ml/kg body weight), a mixture of oxygen and nitrous oxide was given through a mask using a half open system (oxygen 0·8 l/min, nitrous oxide 3–5 l/min, halothane 0·6–0·8%). Endotracheal intubation was not used. The operating microscope was a Zeiss OPMI 6 or OPMI 7 with a 200 mm focal length lens. The instruments used included Castroviejo and Vannas microscissors, O'Brien-Ginch needle-holder with small angulated jaws, Dumont jewellers forceps and Winston special tubal clamps with a diameter of 0·7–1 mm. Suture material was 11/0 nylon.

The animal was placed in a supine position and the lower abdominal quadrant was shaved. The operation was performed under clean but not sterile conditions.

The tubal segment to be operated upon was delivered through a flank incision and placed on a small operation table which depressed the lower border of the incision. The oviduct was placed on a silicone sheet and a few wet swabs protected the intestines which were gently pushed back. As soon as the abdomen was opened, a continuous irrigation system with warm Hartman solution (37°C) was installed to prevent the tissues from drying.

The anastomosis was performed on the isthmus. Under high-power magnifications, the blood vessels in the upper mesosalpinx were coagulated with a Met-Fisher bipolar device using minimal current intensity. A linear cut in the mesosalpinx gave access to the oviduct itself. Vannas scissors were used to make a small incision in the tubal mesentery at the site of anastomosis. Winston tubal clamps of suitable diameter were applied across the oviduct. The oviduct was transected with Castroviejo scissors and both cut ends were washed. Bipolar coagulation was used to obtain good haemostasis. A 0·45-mm-thick polyethylene splint was introinto the tubal lumen to stabilise the oviduct. The stitches were placed in a circular manner. The anterior wall was repaired first, starting from the mesentery. The first stitch of 11/0 nylon was placed deep in the mesentery. When the anterior half of the anastomosis was completed the oviduct was rotated 180° and the posterior wall was sutured. The sutures were placed in the muscle coat without including the mucosa. Seven to eight stitches were sufficient to complete the anastomosis. The mesentery was further closed with two or three supplementary 11/0 nylon stitches. The gap in the mesosalpinx was repaired with four or five stitches of 11/0 nylon. The abdominal cavity was carefully washed with warm Hartman solution and the oviduct was replaced in the abdominal cavity. Ampicillin was given intraperitoneally and the wound was closed in three layers.

Postoperatively the rabbit recovered in a warm cage and received unlimited water. Feeding was started the next morning and antibiotics were given intramuscularly for 3 days.

Investigation of tubo-ovarian function

Three weeks after the operation the animals were mated three times with a buck of proven fertility. Ten days later under Hypnorm general anaesthesia the rabbits were laparoscoped with a children's laparoscope and the following observations were made.

Corpora lutea. Through the laparoscope the number of ova released from each ovary was counted and the mean (SD) value was calculated for each group.

Pregnancy rate. The percentage of animals in which one uterine horn contained at least one implantation was calculated for each experimental group. The operated oviduct and uterus were compared with the non-operated control side in the same animal.

Implantations. The number of blastocysts implanted in each uterus were counted and mean (SD) value was calculated for each group on the operated and control side.

Nidation index. This is the percentage of ova that have become implanted and was calculted as the number of implantations divided by the number of corpora lutea×100.

Implantation failure index (IFI). This is expressed as the difference between the number of non-implanted ova on the operated side (OP) and that on the control side (CO) and was calculated as follows: IFI =

$$\sum \frac{(\text{corpora lutea}-\text{implantations})\text{OP}-(\text{corpora lutea}-\text{implantations})\text{CO}}{n}$$

Adhesions. These were assessed according to Winston (1974) and were classified as: none (−), when no adhesions were visible under magnification; mild (+), when some adhesions were visible with the operating microscope only and at the level of the anastomosis for <5 mm in either direction; moderate (++), when some adhesions could be seen with the naked eye and when adjacent parts of the oviduct or its mesentery were involved; or severe (+++) when the adhesions extended to the uterus, bladder, intestine or abdominal wall.

The χ^2 test, analysis of variance, Student's *t* and Sign test were used to test the significance of the results.

Results

The mean number of corpora lutea, within each group, did not differ significantly between the operated and the control sides except in group 4 where the mean number was 4·1 (SD 0·4) on the operated side and 5·3 (SD 0·5) on the control side (P<0.05). Taking all five groups together the mean number of corpora lutea on the control sides was statistically significantly higher (P<0·001) than that on the operated sides.

The pregnancy rate on the control side was 92% in group 1, 93% in group 2 and 100% in groups 3, 4 and 5. On the operated side the pregnancy rate was 46% in group 1, 67% in group 2, 80% in group 3 and 100% in groups 4 and 5. In group 1, the pregnancy rate on the operated side was significantly lower than on the control side (P<0·05). Overall the improvement of the pregnancy rate on the operated side was also statistically significant (χ^2_1 = 17·93; P<0·01).

There was a significant difference in the nidation index between the operated side and the control side in group 1 (P<0·01) and in group 2 (P<0·05).

The efficiency of the tubo-ovarian unit, expressed by the implantation failure index, was −2·27 (SD 0·71) in group 1, −0·93 (SD 0·66) in group 2, −0·87 (SD 0·86) in group 3, −0·13 (SD 0·48) in group 4 and +0·55 (SD 0·48) in group 5. By linear extrapolation the implantation failure index was zero at anastomosis 106.

The degree of adhesions on the operated side compared with the control side was statistically different in groups 1, 2 and 3 In groups 4 and 5 the difference was not significant. The adhesion formation on the operated side decreased significantly with training ($\chi^2_3 = 26{\cdot}33$; $P<0{\cdot}0001$)

Discussion

Since the introduction of microsurgery in gynaecology high pregnancy rates have been reported after tubal anastomosis, particularly for reversal of sterilization. Most of these series were reported by highly experienced surgeons (Gomel 1977; Winston *et al.* 1979) with a large experience of similar animal work. The present study was designed to investigate the progress of an experienced surgeon with basic experience in microsurgery during a long training programme in experimental tubal microsurgery.

Restoration of the normal tubo-ovarian function was obtained reliably only after over 100 anastomoses had been performed. The failures during the initial stages were due not only to inadequate restoration of patency but also to iatrogenic trauma to the non-operated side as shown by the presence of adhesions and ovulatory disturbance. This degree of trauma is not well reflected by the pregnancy rate. Table 1 shows that, in this experimental model, the nidation index is the more sensitive parameter as it takes into account the interference with the ovulatory function on the operated side. The implantation failure index is probably the most sensitive parameter for assessing preservation of the normal reproductive function as it also takes into account the ovulatory function of the non-operated side. The trauma to the non-operated side may have been due to unnecessary manipulation and prolonged exposure of the abdominal cavity. In man pregnancy rates can also be misleading when different series are compared and the use of cumulative pregnancy rates using life table methodology has been strongly advocated (Querleu 1981; Gulsick & Rock 1981).

It is clear that the availability of an operating microscope is no guarantee of atraumatic and function-restoring surgery.

Microsurgical workshops are organized around the world that offer short courses. It is unrealistic to think that a short experience in experimental work is sufficient for training in microsurgery.

Experience in applying the principles of atraumatic surgery is the most important condition to achieve good results in female infertility surgery. Magnification is undoubtedly helpful for the experienced surgeon to achieve the ultimate in fallopian tube surgery.

Table 1. Tubo-ovarian function after oviduct microsurgery in a series of training conducted in five groups of rabbits ($n = 15$ in each group)

Group	Number of corpora lutea		Pregnancy rate (%)		Number of implantations	Nidation index		Degree of adhesions −	+	++	+++		IFI*
1 OP	3·9 (2·2)	NS	46	$P<0{\cdot}05$	1·1 (1·6)	25 (35)	$P<0{\cdot}01$	4	6	1	4	$P<0{\cdot}001$	−2·27
CO	4·1 (3.0)		92		3·5 (2·5)	75 (40)		12	3	0	0		
2 OP	3·8 (1·5)	NS	67	NS	1·3 (1.6)	37 (37)	$P<0{\cdot}05$	4	5	4	2	$P<0{\cdot}001$	−0·93
CO	4·4 (1·4)		93		2·8 (1·7)	69 (35)		12	0	2	1		
3 OP	4·4 (1·8)	NS	87	NS	2·1 (1·6)	50 (34)	NS	4	9	1	0	$P<0{\cdot}01$	−0·87
CO	5·6 (2·0)		100		4·1 (2·3)	76 (32)		12	1	2	0		
4 OP	4·1 (1·5)	$P<0{\cdot}05$	100	NS	2·5 (1·4)	67 (32)	NS	12	1	2	0	NS	−0·13
CO	5·3 (2·1)		100		3·8 (2·2)	73 (32)		12	3	0	0		
5 OP	5·3 (1·5)	NS	100	NS	4·6 (1·5)	85 (19)	NS	12	3	0	0	NS	+0·55
CO	5·3 (2·1)		100		4·1 (2·1)	77 (28)		15	0	0	0		

Results are means (SD) where appropriate.

OP, operated side, CO, control side, non-operated

* IFI, Implantation failure index, by linear extrapolation the IFI was zero at anastomoses 106.

Acknowledgment

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Clinical implications for immunoscintigraphy in patients with ovarian malignancy: a preliminary study using monoclonal antibody 791T/36

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Summary. Twelve patients with suspected primary and recurrent carcinoma of the ovary have undergone immunoscintigraphy with an anti-tumour monoclonal antibody in order to assess the impact of the technique on patient management. Consistent tumour uptake of radiolabelled antibody was visualized in malignant tumours after subtraction of the blood background activity. Eight patients were imaged before surgery and in all of these the sites of uptake visualized on the images agreed with the surgical findings. In one patient with recurrent disease the imaging information was used as an aid for establishing the extent of external beam radiotherapy. A repeat study in this patient 6 months later revealed a reduction in the size of the tumour, which still concentrated labelled antibody and confirmed the viability of repeat investigations. Immunoscintigraphy was capable of providing diagnostic information which may offer an alternative to second-look surgery in these patients.

Immunoscintigraphy using radiolabelled antibodies is a promising technique for tumour detection (Goldenberg *et al.* 1978). This approach has become more attractive following the production of monoclonal antibodies which react with human tumours (Baldwin *et al.* 1981). One monoclonal antibody, designated 791T/36, prepared against osteogenic sarcoma cells has been used to image primary osteogenic sarcoma following ^{131}I-labelling (Farrands *et al.* 1983). This radioiodine-labelled antibody has also been used to image both primary and metastatic colorectal carcinomas (Farrands *et al.* 1982). Reaction of colorectal carcinoma tissue with this antibody has been assessed using immunohistological techniques, and in addition, autoradiography has been carried out on tumour specimens from patients infused with ^{131}I-labelled material. Both techniques indicate that the antibody reacts primarily with tumour stromal elements and gland secretions, rather than directly with malignant cells (Armitage *et al.* 1984). In view of these findings a preliminary study with ^{131}I-labelled 791T/36 antibody has been made in patients with suspected primary and recurrent ovarian carcinoma, to assess the value of immunoscintigraphy in the diagnosis and management of these patients.

Patients and methods

Twelve patients with clinically suspected primary or recurrent carcinoma of the ovary were investigated. In each patient the extent of

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disease was not known before the antibody investigation and the extent to which their tumours would react with the antibody was unknown at the time of patient selection. Eight patients were imaged before surgery which, in most cases, was a second-look procedure for recurrent disease. The remaining four patients had previously diagnosed ovarian carcinoma and widespread metastatic disease.

Table 1 summarizes the details of the 12 patients. Six patients had adenocarcinoma of the ovary and a seventh patient had a tumour which was initially considered to be a benign mucinous cystadenoma but was subsequently considered malignant. Two patients had recurrent granulosa cell carcinomas and one had a squamous cell carcinoma arising in a dermoid cyst. One patient was found to have a primary mucus-secreting

Table 1. Patient details and imaging results showing sites of antibody uptake and tumour to normal tissue (T:NT) ratios of antibody uptake

Patient	Age (years)	Patient details	Imaging time (h after injection)	Imaging results: Sites of positive uptake after subtraction	Imaging results: T:NT ratios before subtraction
1	54	Recurrent ovarian cystadenocarcinoma for radiotherapy	48	Large area in pelvis and left lower abdomen	2·0·1
1a (repeat study		6 months follow-up after radiotherapy	48	Reduced area in pelvis and lower abdomen	1·7:1
2	37	Recurrent granulosa cell carcinoma of ovary	48	Pelvis	1·6:1
3	31	Massive recurrence of poorly differentiated adenocarcinoma of ovary (?2 from GI tract)	48	Left abdomen	1·0·1
4	52	Recurrent disease previously diagnosed as benign mass which had been removed (specimen taken)	48	Pelvis	1·5.1
4a (repeat study)		5 months follow-up after surgery	48	Pelvis	1·2.1
5	72	Bilateral ovarian carcinoma, poorly differentiated papillary serous cystadenocarcinoma with metastasis in omentum, ascites, cyclophosphamide	48	Pelvis	1 2.1
6	48	Simple serous cysts in residual ovarian tissue	48	None	—
7	51	Mucus secreting adenocarcinoma ? pancreatic in origin All tumour in the upper abdomen with ascites++	24	Stomach region*	—
8	40	Recurrent granulosa cell carcinoma with multiple deposits on large bowel	48	Pelvis and abdomen	1·5 1
9	49	Serous cystadenocarcinoma resected June 1980. Evidence of large pelvic recurrence	48	Pelvis and left lower abdomen	1·2.1
10	83	Squamous cell carcinoma arising from a teratoma of the ovary and involving bowel	18	Widespread in abdomen and pelvis	1·0 1
			144	Ditto	1·3:1
11	35	Ovarian carcinoma, bilateral salpingo-oophorectomy and hysterectomy	48	Pelvis	1·2:1
12	46	Ovarian carcinoma of borderline malignancy with recurrent ascites	48	Pelvis	1·0 1

* ? Uptake in pancreatic tumour or free ^{131}I in stomach

adenocarcinoma probably arising in the pancreas and not involving the pelvic organs. One patient had a benign serous cyst in an ovarian remnant following pelvic clearance.

All patients gave their informed consent before the administration of the labelled antibody.

Antibody and labelling

Monoclonal antibody 791T/36 (mouse Ig G_2b) (Embleton *et al.* 1981) was isolated from murine ascitic fluid by affinity chromatography on Sepharose-Protein A as described previously (Pimm *et al.* 1982). Purified pyrogen-free antibody was labelled with ^{131}I using an iodogen method (Pimm *et al.* 1982), the preparations used for infusion containing 0·2 mg protein. Preparations were diluted in saline and sterilized by Millipore filtration.

Antibody administration

To prevent thyroid uptake of free radioiodide, patients received 60 mg potassium iodide per day for 2 weeks starting 24 h before the infusion of the antibody; 1 ml of ^{131}I-labelled antibody solution was injected subcutaneously into the left arm of each patient 30 min before the infusion of the antibody to test for anaphylaxis, and subsequently 20 ml of solution containing 70 MBq ^{131}I-labelled antibody was injected into an antecubital vein of the right arm.

All patients tolerated the procedure well with no adverse reactions.

Imaging

Patients were imaged between 18 and 48 h after administration of the ^{131}I-labelled antibody with one patient undergoing repeat imaging at 6 days. Anterior and posterior images of the abdomen and pelvic regions were acquired using a gamma camera having a 40 cm field of view, and data were stored by computer. A 5-min acquisition generally contained between 100 000 and 150 000 counts in the ^{131}I views. ^{99m}Tc-labelled erythrocytes and free pertechnetate were used to simulate the distribution of the labelled antibody remaining in circulation. Each ^{99m}Tc image contained approximately 200 000 counts. Background subtraction was carried out as described by DeLand *et al.* (1980). Additional data processing was carried out to reduce the artefacts resulting from the differential septal penetration and scatter of the radionuclides used. A detailed description of the image processing techniques used in the present study has been reported previously (Perkins *et al.* 1984). Regions of interest were defined on the images around areas of abnormal uptake seen on the corrected images and around non-tumour sites. Target to non-target ratios (T:NT) were calculated from the antibody images before subtraction.

Results

Uptake of labelled antibody was demonstrated at the tumour site in 11 out of the 12 patients investigated. For five patients only, tumour uptake of antibody could be visualized on the ^{131}I images before subtraction. Viewing of the blood background image provided additional information regarding the disruption of normal anatomy by the tumour. A relatively high count rate was recorded from the urinary bladder of most patients but the amount of radioiodine excreted in urine was not measured. Since the counts from the bladder tended to obscure the antibody distribution in adjacent tissues it was necessary to define a computer mask over the bladder image to remove completely the counts from this region. When expressed as a T:NT ratio the uptake ranged from 1·0:1 to 2·0:1 before image subtraction. These values are similar to those measured using the same antibody in patients with colorectal tumours where Armitage *et al.* (1984) showed that in colorectal cancer the uptake of this antibody was three times that of normal mouse immunoglobulin In the patients with low T:NT ratios, background subtraction was essential in order to visualize abnormal uptake. Experience with this labelled antibody in other patients has led to the recognition of false-positive results. This has been reported by Green *et al.* (1984) who developed a set of empirical rules for the interpretation of subtraction images. One patient (no. 6) in whom the antibody failed to localize was later proven to have a benign mass. In another patient (no. 7) intense activity was demonstrated in the region of the stomach which may have been due to free radioiodide. This patient was subsequently found to have a massive tumour with metastasis in the epigastrium which was thought to be pancreatic in origin.

In all cases with malignant disease the tumour was imaged with the antibody irrespective of the

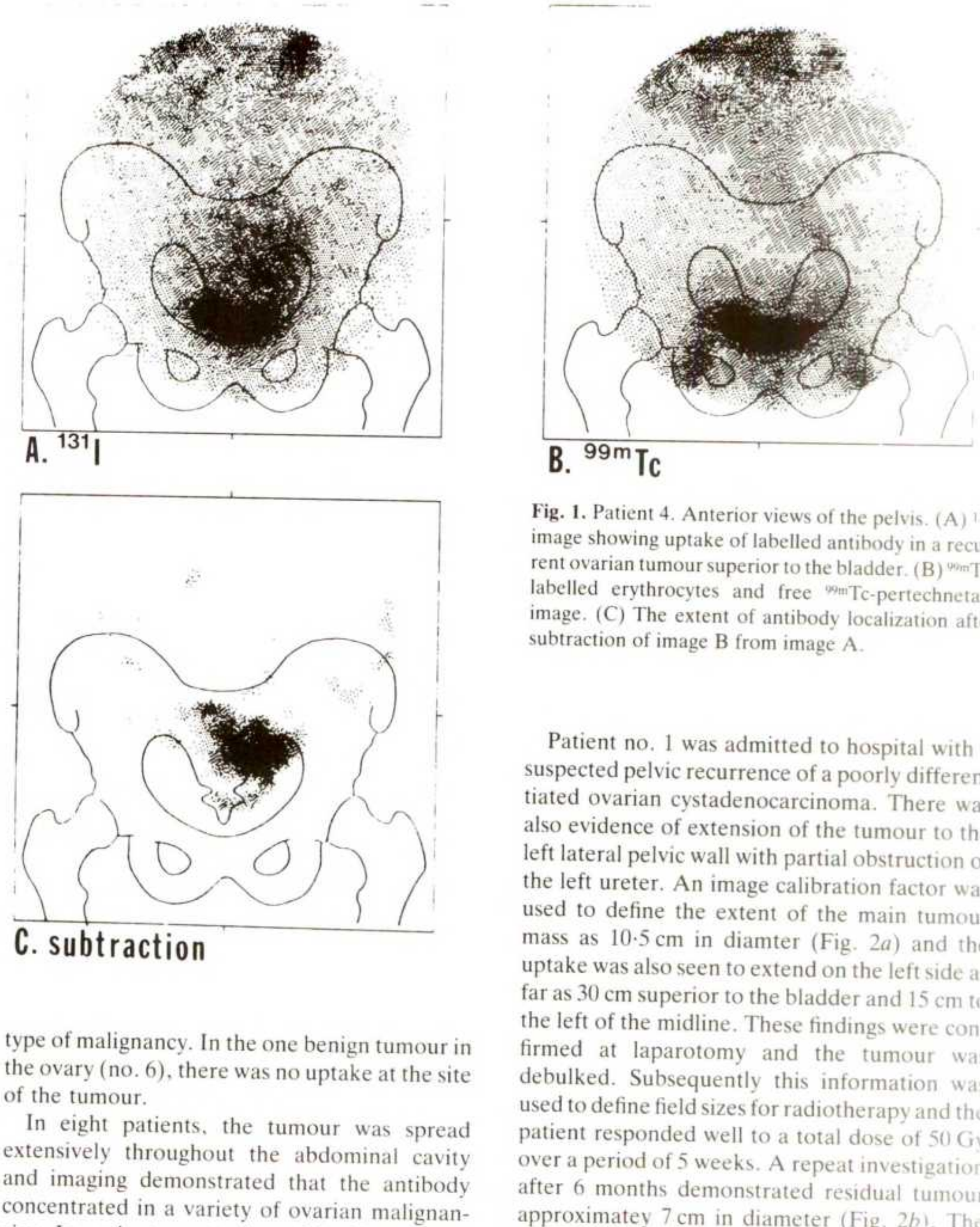


Fig. 1. Patient 4. Anterior views of the pelvis. (A) ^{131}I image showing uptake of labelled antibody in a recurrent ovarian tumour superior to the bladder. (B) ^{99m}Tc-labelled erythrocytes and free ^{99m}Tc-pertechnetate image. (C) The extent of antibody localization after subtraction of image B from image A.

type of malignancy. In the one benign tumour in the ovary (no. 6), there was no uptake at the site of the tumour.

In eight patients, the tumour was spread extensively throughout the abdominal cavity and imaging demonstrated that the antibody concentrated in a variety of ovarian malignancies. In patient no. 4, the original lesion was thought to be a benign mucinous cystadenoma, but recurrence occurred 6 months later and a positive uptake (Fig. 1) of 1·5:1 prompted a clinical review of the diagnosis. The recurrent tumour was debulked and subsequently a histological diagnosis of mucinous cystadenocarcinoma was made. A repeat study in this patient 5 months after surgery has showed further pelvic recurrence.

Patient no. 1 was admitted to hospital with a suspected pelvic recurrence of a poorly differentiated ovarian cystadenocarcinoma. There was also evidence of extension of the tumour to the left lateral pelvic wall with partial obstruction of the left ureter. An image calibration factor was used to define the extent of the main tumour mass as 10·5 cm in diamter (Fig. 2*a*) and the uptake was also seen to extend on the left side as far as 30 cm superior to the bladder and 15 cm to the left of the midline. These findings were confirmed at laparotomy and the tumour was debulked. Subsequently this information was used to define field sizes for radiotherapy and the patient responded well to a total dose of 50 Gy over a period of 5 weeks. A repeat investigation after 6 months demonstrated residual tumour approximatey 7 cm in diameter (Fig. 2*b*). The T:NT uptake was reduced slightly from 2·0:1 to 1·7:1.

Patient no. 10 presented with subacute bowel obstruction and a mass palpable to the pelvis. Imaging after subtraction showed localization of labelled antibody in the pelvis and lower abdomen (Fig. 3) and a pre-operative diagnosis of malignant disease was suspected. At laparotomy an ovarian tumour involving the left ovary and sigmoid colon was revealed and bilateral sal-

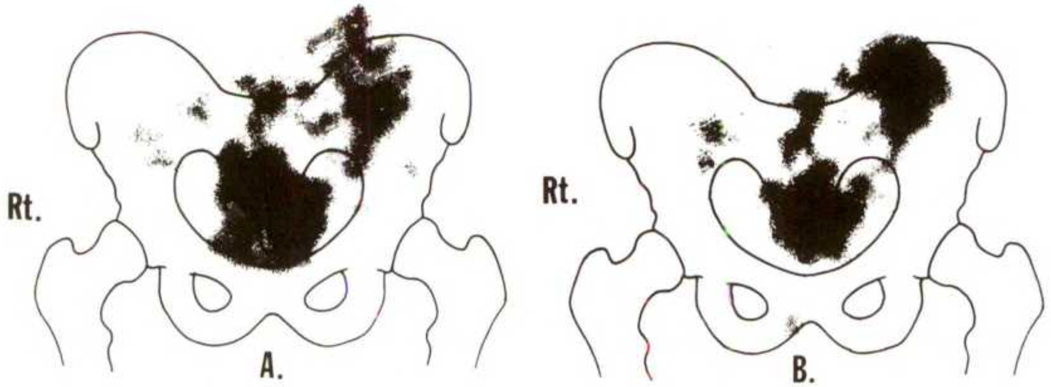
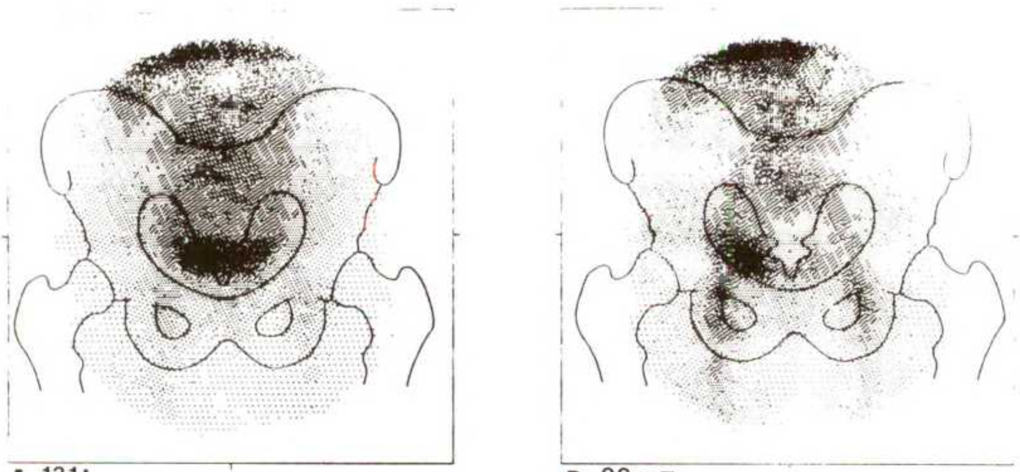


Fig. 2. Patient 1. Anterior views of the pelvis. (A) Background subtracted image showing the extent of labelled antibody uptake in a recurrent ovarian cystadenocarcinoma. (B) Follow-up study 6 months after surgery and radiotherapy showing residual tumour.


A. ^{131}I

B. ^{99m}Tc

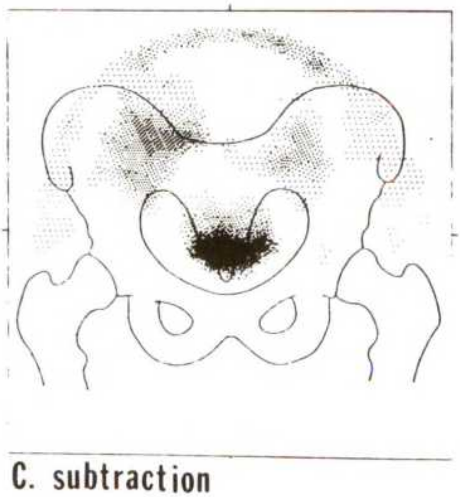

C. subtraction

Fig. 3. Patient 10. Anterior views of the pelvis. (A) ^{131}I image. (B) ^{99m}Tc background image showing the position of the bladder displaced to the right of the pelvis by a large dermoid cyst. (C) Distribution of antibody in a squamous cell carcinoma after subtraction of the blood background and bladder activity.

pingo-oophorectomy, hysterectomy and resection of the sigmoid colon was performed. The tumour was shown to be a squamous cell carcinoma arising in a dermoid cyst.

Discussion

The pattern of tumour expression of antigens defined by monoclonal antibodies is such that one antibody type can often be used to localize in a variety of malignancies. Monoclonal antibodies including those to carcinoembryonic antigen and milk fat globule have been shown previously to localize in ovarian carcinoma (Mach *et al.* 1981; Epenetos *et al.* 1982). In this study we have used a monoclonal antibody originally raised to an osteosarcoma cell line to image malignant lesions of ovarian origin. In one patient in whom the lesion was initially considered histologically to be benign, the uptake of the antibody suggested that the lesion was malignant. Subsequent histological examination of the tumour recurrence confirmed the malignant nature of this lesion.

The antibody appears to image malignant tumours irrespective of their cellular origin but it did not localize in the one benign tumour studied. In two patients, the imaging has been repeated approximately 6 months after initial surgery and/or radiotherapy to the original lesion and has demonstrated persistence of the tumour which was not clinically apparent. The localization of tumour sites by labelled anti-tumour antibody aided radiotherapy treatment planning for one patient and may in future provide a technique whereby it is possible to localize recurrences of ovarian carcinoma without 'second look' surgical procedure and to focus therapy in the recurrent tumour site. Futhermore, in these particular cases, measurement of the T:NT ratios may provide an indication of tumour response to therapy.

The present methods of assessment of tumour response in ovarian carcinomata are generally unsatisfactory and this study has demonstrated in one patient that immunoscintigraphy was an accurate technique for quantifying tumour response to therapy. Furthermore the localization of labelled antibody in tumours of various cellular origin suggests that the antibody binds to an antigen that is specific to malignant ovarian tumours generally, rather than to the cell membrane of a specific tumour type. The potential value of such an antibody is apparent in the localization of recurrent tumour and in the direction of radiotherapy for the treatment of secondary deposits. It also provides methods for the assessment of response to tumour therapy and the localization of secondary deposits without the application of second-look procedures with their accompanying morbidity in the older age group patients. The present study indicates a potential for this technique in differentiating between malignant and non-malignant tumours, particularly in cases where the histological diagnosis is equivocal.

The antibody reported in this study has exhibited a high affinity for ovarian malignancies of various types with significant uptake of the antibody in all 10 of the malignancies arising from the ovary. The antibody also imaged one tumour of probable pancreatic origin, but did not image the benign ovarian cyst included in the study. Thus, it appears to have a high degree of reliability in imaging malignant disease. Two patients have had successfully repeated investigations after approximately 6 months. The nature of the tumours included in this initial study did not allow us to provide data on the level of discrimination for tumour deposits but it is planned to examine patients with known ovarian carcinoma before second-look procedures. This technique may subsequently remove the need for these procedures.

Acknowledgments

We thank Drs Martin Wastie and Hazel Price for their co-operation in obtaining certificates of authorization to administer the radiolabelled antibody to human subjects, Mrs R. A. Marksman for routine radioiodination of antibody and the Medical Physics Technicians in Nuclear Medicine at University Hospital. This work was supported by the Cancer Research campaign.

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Radionuclide imaging of ovarian tumours with ^{123}I-labelled monoclonal antibody (NDOG$_2$) directed against placental alkaline phosphatase

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Summary. A radiolabelled monoclonal antibody (NDOG$_2$) directed against placental alkaline phosphatase (PLAP) was used in the radioimmunodetection of ovarian carcinoma. Tumour deposits were successfully visualized in 11 of 15 patients and the abnormalities demonstrated were classified as focal or diffuse. Of the 11 patients, eight showed focal abnormalities alone and three had a diffuse abnormality, of which two also showed a focal abnormality. False-positive results may occur not only due to uptake of ^{123}I by gut mucosa and an inadequately blocked thyroid gland but also from activity in an incompletely emptied bladder. A false-negative result occurred due to high background activity in the liver masking a known, discrete tumour deposit.

The use of monoclonal and polyclonal antibodies in radioimmunodetection offer potential in the diagnosis of carcinoma. A monoclonal antibody is a defined chemical entity recognizing a specific antigenic determinant (Milstein 1982), whereas polyclonal antiserum, even when affinity-purified, is a mixture of antibodies, recognizing a variety of different determinants of a particular antigen, and whose composition may vary from batch to batch. The purity of monoclonal antibodies and their high specific activity, which can be as high as 95% (Mason & Williams 1980) give them theoretical advantages over polyclonal antisera, although radiolabelled antibodies of either type have been successfully used to demonstrate breast (Rainsbury *et al* 1983), bowel (Goldenberg *et al.* 1980) and melanoma (Larson *et al* 1983) tumour deposits by radionuclide imaging.

The radioimmunodetection of ovarian tumours has been successfully achieved using polyclonal antibodies to carcinoembryonic antigen (Van Nagell *et al.* 1980), and α-fetoprotein (Halsall *et al.* 1981) and a monoclonal antibody to human milk fat globule membrane antigen (Epenetos *et al.* 1982) The radionuclide used in these studies was either iodine-123 (^{123}I), or iodine-131 (^{131}I). The radionuclide ^{123}I has a principal gamma photon energy (0·159 MeV) well suited to the design and optimum performance of modern gamma cameras, although the physical half-life (13 h) may be less than optimal for some applications of monitoring changing biodistributions. On the other hand, ^{131}I has a relatively long physical half-life (8·05 days) but the

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decay scheme and photon energy of the principal absorption peak (0·364 MeV) make this a less desirable radionuclide for imaging purposes.

Ectopic synthesis of placental alkaline phosphatase (PLAP) by cancer cells was first reported 16 years ago (Fishman *et al.* 1968). PLAP is a dimeric, membrane-bound enzyme with each subunit having a molecular weight of 65 000 (Millan *et al.* 1982). The enzyme exists in three common allelic forms but there are over 40 rare variants known (Donald & Robson 1974). PLAP has been found in the sera of patients with a variety of tumours including ovarian cancer, and between 32% (Van Nagell *et al.* 1981) and 35% (McLaughlin *et al.* 1983) of patients in this group have raised serum levels of PLAP.

The monoclonal antibody, $NDOG_2$, is a class IgG2b immunoglobulin specific to PLAP (Sunderland *et al.* 1981) and recognizes the three common allelic forms of PLAP (Sunderland *et al.* 1984). Using $NDOG_2$ in an indirect immunoperoxidase staining technique, PLAP has been demonstrated, to varying degrees, in normal thymus, cervical, endometrical, endometrial and fallopian tube epithelium and in trace amounts in lung alveoli. In addition 70% of ovarian cystadenocarcinomata show significant $NDOG_2$ staining (Sunderland *et al.* 1984).

This paper describes the preparation and use of ^{123}I-labelled $NDOG_2$ (^{123}I-$NDOG_2$) in the radioimmunodetection of tumour deposits in 15 patients with suspected ovarian carcinoma.

Patients and methods

Patients

All patients gave informed consent to radionuclide imaging and this project was approved by the Bristol and Weston District ethical committee.

Fifteen patients with suspected or confirmed ovarian carcinoma were included in this study. Many of the patients were, or had been, on a regimen of chemotherapy and/or radiotherapy.

Eleven patients were selected for radionuclide imaging on the basis that their tumour-expressed PLAP, but four patients were radioimaged without knowing the PLAP status of their tumour.

Expression of PLAP was determined by immunohistological staining of the tumour tissue alone in five patients, by serum assay alone in two patients or by both methods in four patients.

In all patients the biodistribution of ^{123}I-$NDOG_2$ was correlated with operative findings, X-ray computed tomography (CT) or ultrasound scanning (USS).

Thirteen patients were imaged post-operatively and two pre-operatively.

Preparation of $NDOG_2$ antibody

The $NDOG_2$ cell line was derived from a fusion between NSI myeloma cells and spleen cells from mice immunized with human placental syncytiotrophoblast (Sunderland *et al.* 1981). Monoclonal antibody was obtained by growth of $NDOG_2$ cells as ascites tumours in BALB/c mice or in cell culture. The monoclonal antibody was purified by protein A-conjugated sepharose CL4B (Sigma) affinity chromatography, followed by gel filtration on Sephacryl S200 in phosphate-buffered saline (PBS) (Oxoid Dulbecco A), divided into 250-μg aliquots and stored at −20°C until use. The preparation gave no toxic effects when injected into two rats and two guinea-pigs at a dose of 70-μg per animal. Purity was confirmed by polyacrylamide gel electrophoresis in sodium dodecyl sulphate.

Immunohistology

Tissue obtained at operation was frozen in liquid nitrogen within 2 h of collection and then stored at −70°C. Frozen sections of 6-μm thickness were cut and stained using an indirect immunoperoxidase method (Sunderland *et al.* 1984).

The strength of staining was assessed according to the percentage of neoplastic epithelial cells reacting positively and were graded as follows: grade 1, <1%; grade 2, 1–25%; grade 3, 25–75%; and grade 4, 75–100%.

Serum assay

This microtitre plate assay has been developed by McLaughlin *et al.* (1983) for use with a similar monoclonal antibody. The upper limit of normal, using $NDOG_2$, in non-smokers, is 0·28 i.u./l. In 67% of smokers, serum PLAP was elevated; this result did not bear any relation to the number of cigarettes admitted to being smoked per day.

Labelling of $NDOG_2$

Conjugation of ^{123}I to $NDOG_2$ was achieved by a modification of the standard chloramine T procedure (Hunter & Greenwood 1962). A 500-mBq sample of dry sodium 123-iodide (Harwell) with carrier sodium hydroxide was dissolved in 0·2 ml of 0·3 M Sodium phosphate pH 7·2 (BDH analar), and 0·3 ml PBS. A 100-μl volume of $NDOG_2$ antibody, at 2·6 mg/ml in PBS, was then added, followed by 100-μl chloramine T at 2 mg/ml in 0·3 M sodium phosphate pH 7·2. The iodination was allowed to proceed for 5 min with intermittent mixing and the reaction stopped by addition of 100-μl saturated L-tyrosine in 0·3 M sodium phosphate pH 7·2. A 100-μl volume of human plasma protein fraction (HPPF) was then added as a carrier, and the free iodide and ^{123}I-$NDOG_2$ separated by chromatography on a 10-ml sephadex G50 column in PBS. A 20–30% yield of radioactivity was obtained in the ^{123}I-$NDOG_2$ fraction, giving a specific activity of 4–8 mCi/mg $NDOG_2$.

The preparation was made up to a convenient injection volume with normal saline. All materials and reagents were sterilized before use and the entire procedure was carried out in the sterile radioisotopes suite at the Bristol General Hospital. The final preparation was filtered through a 0·2-μm filter into the injection vial. The percentage free iodine in the product was assessed by chromatography in trichloracetic acid prior to injection and varied from <1% to 10%.

Sterility and apyrogenicity were confirmed after preliminary trials. An identical iodination using ^{125}I was shown to give an antibody preparation of which 55–70% was specifically active as shown by binding to fresh placental membrane in the presence of excess normal mouse serum.

Data acquisition

Data were acquired by collecting images of the biodistribution of the radiopharmaceutical over a 20-h period. Each patient received a thyroid blocking agent before the intravenous injection of 40–70 mBq of ^{123}I-$NDOG_2$. Potassium perchlorate, in the dose of 400 mg 1 h before injection and then 200 mg daily for 3 days, was found to be unsatisfactory in suppressing iodine uptake by the thyroid gland. Potassium iodide, 420 mg orally 1 h before injection and then 180 mg daily for 3 days, has since proved to be successsful in blocking the thyroid gland.

Three sets of sequential images were acquired at approximately 10 min (early), 4 h (intermediate) and 20 h (late) after intravenous injection of the labelled antibody. The patient was asked to empty her bladder before imaging on each occasion, and sequential images were obtained of head, thorax, abdomen and pelvis. The equipment used was an International General Electric Maxicamera 400 T and a Link Systems data processor, and the data were collected on a 64 × 64 matrix, with the total number of counts for each image between 300 000 and 600 000.

By computer aided subtraction of early from the later images an attempt was made to enhance the visualization of areas of increased radioactivity. In order to minimize the generation of artefacts and improve the accuracy of the subtraction images, the patient was repositioned before each image by the use of radioactive skin markers placed over the anterior superior iliac crests (Granowska *et al.* 1984).

Results

The findings from radioimmunodetection have been correlated with the results from CT, ultrasound and information obtained at surgery (Table 1). Of the 13 patients who were imaged postoperatively, five patients (nos 3, 5, 9, 11 and 14) were imaged within 1 month and five patients (nos 8, 10, 12, 13 and 15) were imaged within 2 months of the initial operation. Two patients (nos 1 and 6) were imaged 3 months after operation, and a further two patients (nos 2 and 4) were imaged pre-operatively.

We detected raised serum PLAP in 67% of normal subjects, who were cigarette smokers, and in one patient (no. 6) this caused us erroneously to suspect tumour recurrence. In all other cases raised serum PLAP was associated with genuine tumour activity.

Normal features

These reflect the blood pool distribution and in the early images the major blood vessels, heart, liver and spleen are shown clearly. On the subsequent images there are only changes of degree in this distribution with the additional minor activity in the skeleton. In one patient (no. 7) there was no abnormality at any stage, she had residual peritoneal seedling deposits after primary surgery but had completed a course of chemotherapy prior to the investigation. The patient remains well 15 months later, with no evidence of recurrence. Three other patients in

Table 1. Characteristics of 15 patients with suspected ovarian carcinoma

				Findings			
Patient no	Grade of staining	Stage	Serum PLAP (i u./l)	Imaging	Operation	CT	USS
1	G4	III	—	Left pelvic mass	Residual tumour left pelvis	—	Left pelvic mass
2	G2	III	—	Right pelvic mass omental secondary	Corresponded to pre-op imaging findings	—	—
3	G3	III	—	Focal right pelvic sidewall	Residual tumour bladder (right) and colon and parasitic nodes	No masses	—
4	—	0	—	Subtraction false positive pelvic mass	Normal	—	? Pelvic mass
5	—	IV	—	Diffuse abdominopelvic activity	Residual ascites peritoneal seedlings, liver metastasis	—	—
6	G3	IA	0·39	Uptake caecum 4 h no uptake 20 h	No residual tumour after primary surgery	No tumour	—
7	G4	III	—	Normal	Residual peritoneal seedlings, imaged after course of chemotherapy	—	—
8	G3	III	—	Diffuse abdominopelvic activity and focal abnormality in pelvis	Residual tumour on bladder, bowel liver edge	—	Pelvic mass
9	G1	III	0·42	Focal pelvic sidewall	Residual tumour pelvic sidewall and intra-abdominal seedlings, omenectomy performed	—	—
10	—	III	1·6	Focal to omentum and pelvis on subtraction	Carcinoma ovary omental secondaries	Large abdominal mass, pelvic mass	—
11	—	III	Normal	No tumour, uptake by stomach	Residual intraperitoneal seedings	—	—
12	G4	III	—	Focal areas in pelvis	Residual tumour on rectum	—	—
13	G2	IIb	0·80	Two foci; right pelvic sidewall and upper central abdomen	Residual microscopic tumour deposits right pelvic sidewall	Mass in right side of pelvis	—
14	G2	III	1·8	Diffuse abdominopelvic activity; left ovarian tumour seen on subtraction (focal)	Residual left ovarian tumour omental and intraperitoneal secondaries	—	—
15	—	Ic	2·81	Pelvic mass (focal)	Initial macroscopic but not microscopic clearance	Pelvic mass	—

PLAP, Placental alkaline phosphatase; CT, X-ray computed tomography; USS, Ultrasound scanning.

whom no tumour was detected (nos 4, 11 and 6) are discussed below.

Abnormal features

The following abnormal groups were identified at radioimmunoscintigraphy.

Focal abnormalities. These were seen in 10 patients, being present usually in the pelvis and numerous in one instance (no. 12). In patient 10, the abnormalities were greatly enhanced by subtraction (Fig. 1) although this was not always necessary (e.g. patient 9, Fig. 2) and in patients

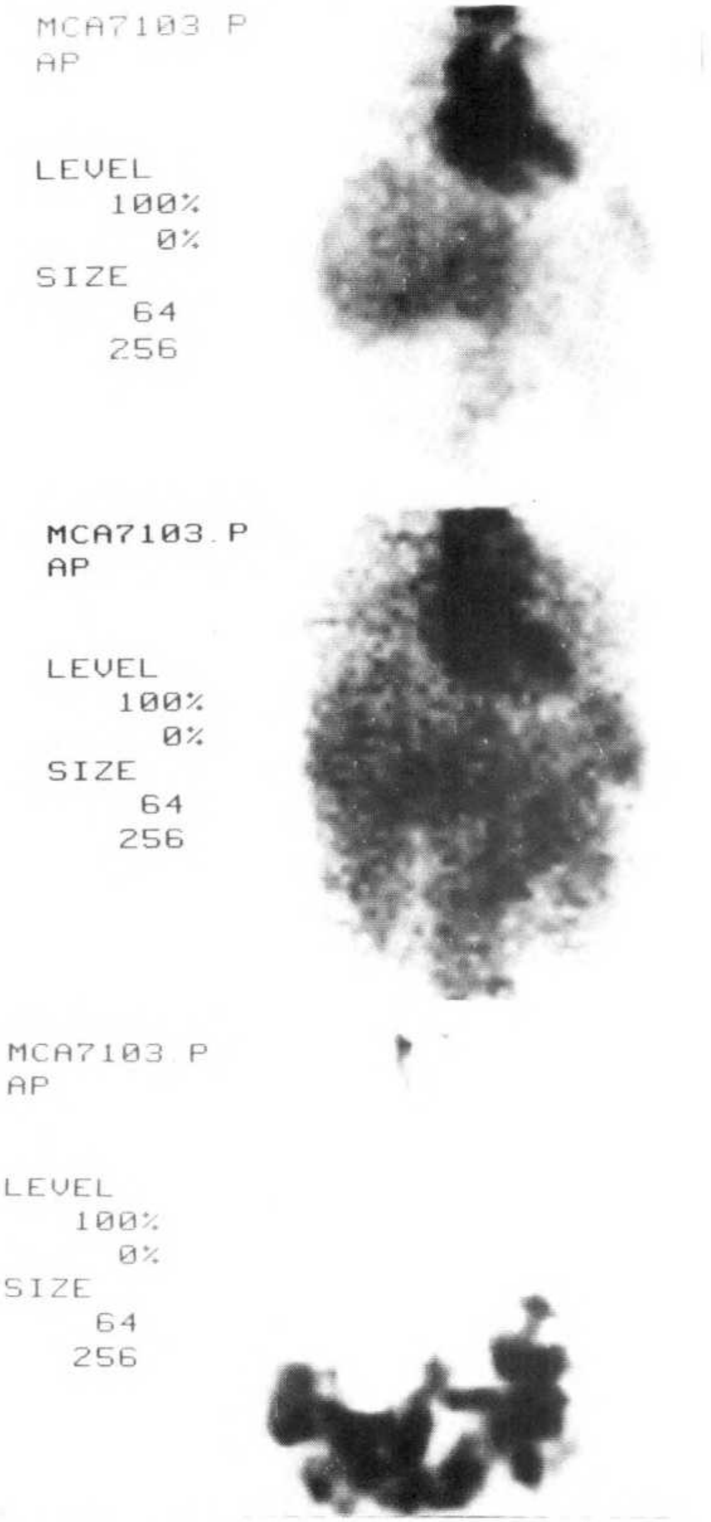

Fig. 1. (*a*) Early image of abdomen. (*b*) Late image of abdomen. (*c*) Subtracted image showing the enhanced image of tumour deposits in omentum (patient 10).

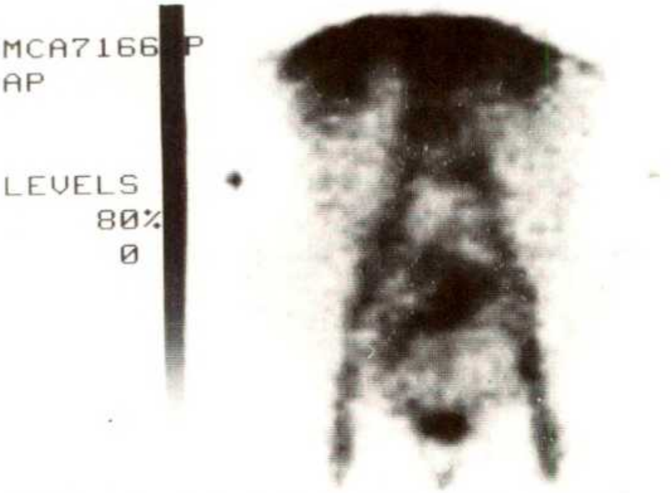

Fig. 2. Non-subtracted image showing pelvic secondary (patient 9).

15 and 13 the abnormalities correlated well with demonstrated tumour on CT scanning (Fig. 3*a*, *b*). In both these patients the site of recurrent tumour was first detected by radioimmunoscintigraphy performed because of raised serum PLAP. In patients 8 and 14 there was also a diffuse abnormality.

Diffuse abnormalities. These were present in three patients, two of whom also had a focal abnormality. In patient 14, who was known to have extensive intraperitoneal seedlings and ascites, the diffuse activity was intense enough to mask the appearances of the major iliac blood vessels (Fig. 4). In another patient (no. 5) a known metastasis in the liver could not be identified by radionuclide imaging.

False-positives and artefacts. Inadequate thyroid blocking with potassium perchlorate resulted in thyroid uptake of free ^{123}I in patients 13 and 11 and it is likely that activity in the upper abdomen in two patients (nos 13 and 11) was due to free ^{123}I uptake in gastric mucosa. Intense activity was noted in the right iliac fossa, in the region of the caecum, in patient 6 on the intermediate image (Fig. 5) but not on the late image. There was no clinical or CT evidence of tumour in the right iliac fossa. Radioactive urine in the bladder, through omitting to get the patient to pass urine prior to late imaging, caused a problem in one patient (no. 15). In patient 4 failure to empty a bladder on the early scan caused a region of apparent increased radioactivity to be generated when this was subtracted from a slightly radioactive but still full bladder on the intermediate image (Fig. 6*a*–*c*).

Discussion

The quality of any image is a compromise between sensitivity and resolution. In the present context the ratio of tumour activity to background is relatively low and the resolution is coarse in order to enable adequate pixel count statistics. In these circumstances background subtraction is a potentially attractive way of improving image quality. Attempts to improve the quality of the image by this technique rely on the precise positioning of the patient on each occasion and this can prove difficult, even with the aid of radioactive skin markers, especially in obese patients. The greatest difficulty in this area of imaging is presented by the bladder and unless it is virtually empty during the time of each imaging, misleading false-positive artefacts can be generated. The present image subtraction techniques do not afford a high level of confidence in areas of relatively high background uptake where the generation of false-positives may be easily obtained. However, subtraction is not always necessary and tumour deposits have been demonstrated clearly without subtraction of early from intermediate or late images. There are two important sites of high background activity; first the liver, where it is normal, and may mask a known deposit; second, in overt ascites with or without numerous peritoneal seedling deposits, where it is itself abnormal and may obscure normal features such as the abdominal vessels. Clearly intense ascitic activity may obscure localized deposits but it did not in fact do so in two present instances.

Artefacts were produced by uptake of free ^{123}I

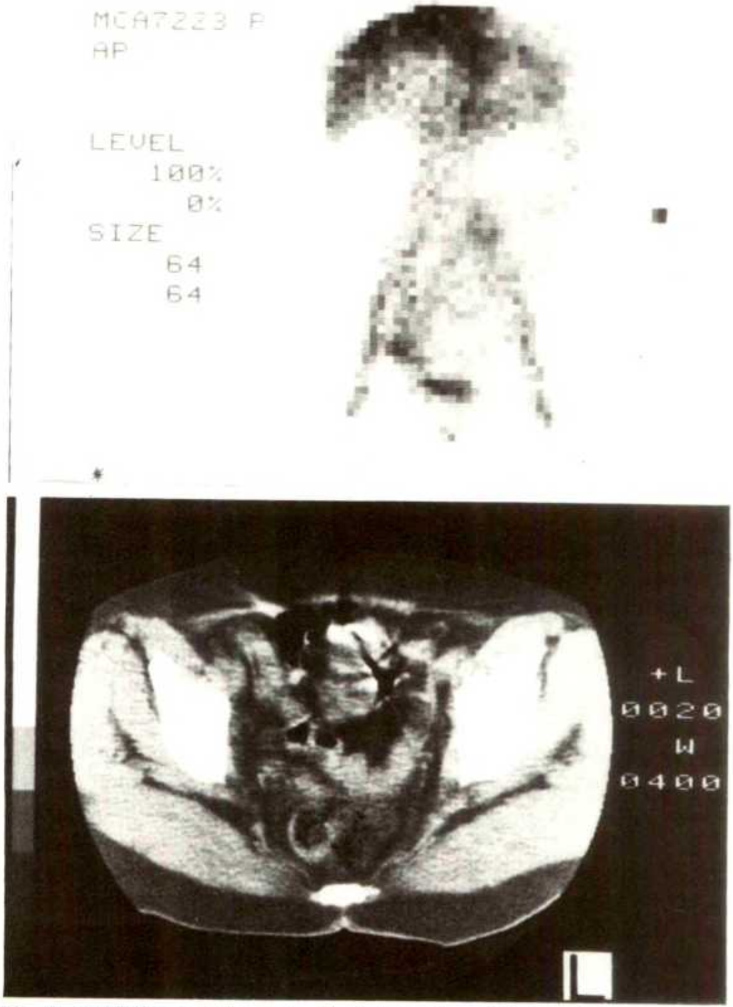

Fig. 3. (*a*) Pelvic secondary visualized by radionuclide imaging (patient 13). (*b*)Pelvic secondary visualized by CT scanning (patient 13).

by stomach and bowel mucosa and by the thyroid gland. Administration of potassium iodide is preferred to potassium perchlorate for blocking thyroid uptake but does not always block that by stomach mucosa.

No tumour deposits were detected by radioimmunoscintigraphy in a further four patients. One of these (no. 7) was probably in remission at the time of imaging and has remained well since. Another patient (no. 11) had residual peritoneal seedling deposits, but her tumour was subsequently shown not to express PLAP. The third patient (no. 6) was imaged because of elevated serum PLAP, the high activity detected in the right iliac fossa was transient and artefactual due to free ^{123}I activity in the caecum. There was no evidence of tumour recurrence and the cause for her elevated PLAP was almost certainly cigarette smoking. This raises the question of the significance of transient activity. The timing of maximum activity varied between patients and it is possible that positive activity will decline during the span of serial images. In this instance the striking change in activity, its location and the normal CT left no doubt about the artefact but the conclusion that declining activity alone is a negative feature should be drawn with caution.

There appeared to be a poor correlation between grade of staining and the radionuclide image obtained. A very clear image was obtained in patient 9 (who had recurrence of a stage 1 tumour) without the need for subtraction (Fig. 2), but the tumour tissue (from an omental

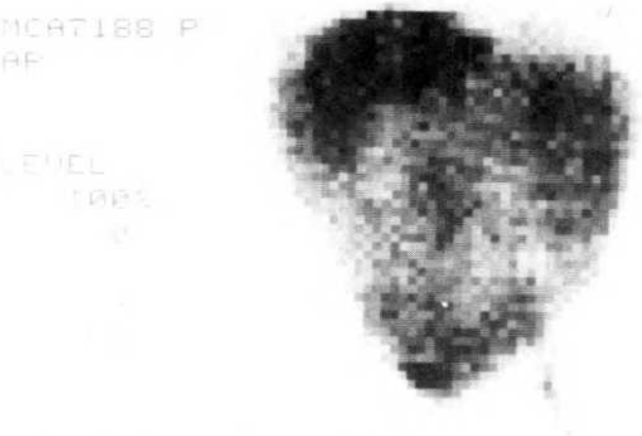

Fig. 4. Pelvic image showing marked diffuse activity (patient 14).

deposit) only stained grade 1 when examined immunohistologically. This suggests either a very high affinity for the tumour cells expressing PLAP by NDOG$_2$, or, as the tissue stained was from an omental secondary not the pelvic secondary visualized at imaging, heterogeneity of expression of PLAP within the various secondaries. This patient had elevated serum PLAP and her pelvic recurrence was detectable on vaginal examination. However, in two patients (nos 13 and 15) recurrent tumour was not clinically obvious but was demonstrated by radioimmunoscintigraphy and confirmed by CT. Raised serum PLAP was the indication for radionuclide imaging in both these patients, and monitoring the progress of patients, with ovarian carcinoma, by serial serum PLAP estimation in combination with radioimmunoscintigraphy, to detect sites of recurrence in those patients with a rising PLAP titre, shows promise in this preliminary study.

CT and USS played a limited part in this pilot study but their use enabled the tentative conclusions to be drawn that the value of a positive scan is enhanced by imaging a corresponding mass, and conversely the absence of a relevant CT or USS lesion may confirm the presence of an artefact. Therefore a longitudinal prospective study has been commenced comparing ultrasound scanning, CT and radionuclide imaging findings, in conjunction with the serum assay for PLAP, with that of surgery, to confirm and

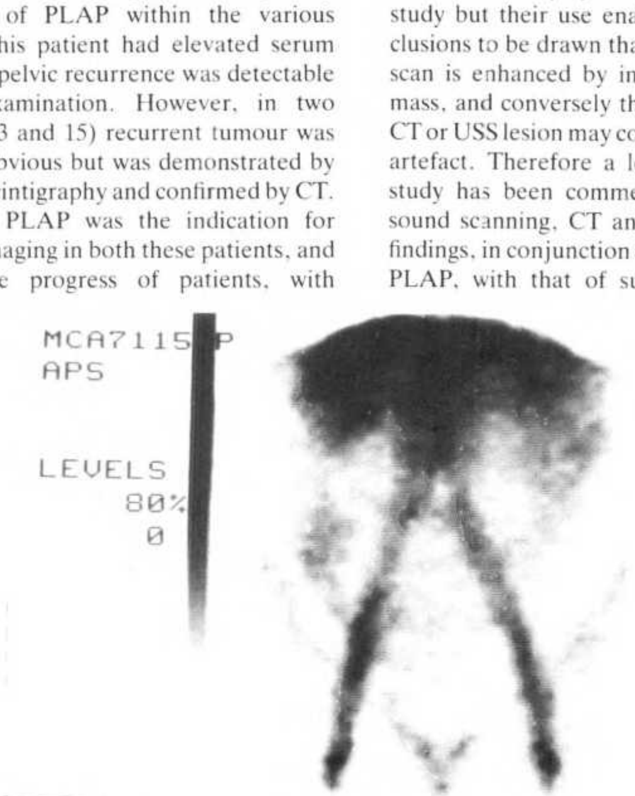

Fig. 5. Intermediate image showing transient caecal activity (patient 6).

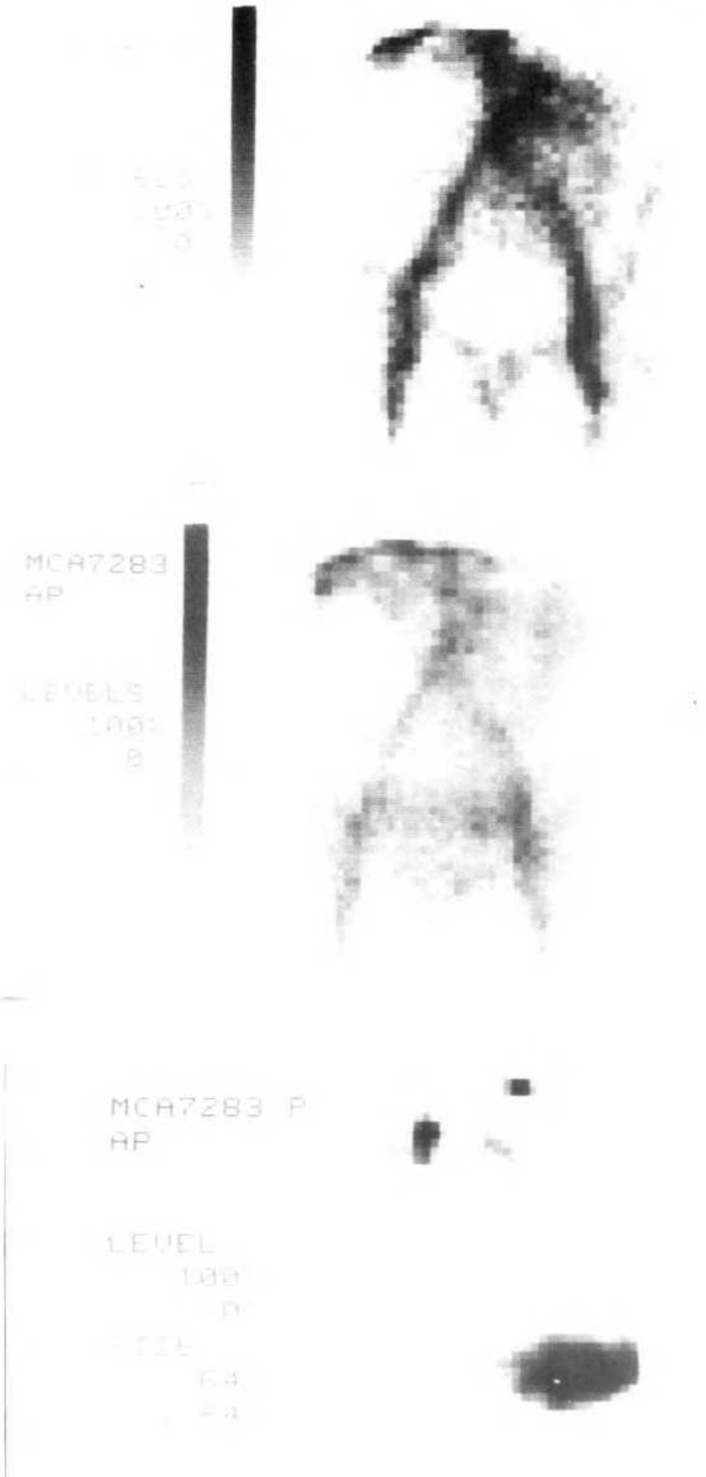

Fig. 6. (*a*) Early pelvic image. (*b*) Intermediate pelvic image. (*c*) Subtracted image showing false-positive 'tumour' (patient 4).

assess the role of radionuclide imaging in the management of patients with ovarian carcinoma.

Acknowledgments

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Topical 5-fluorouracil in the treatment of vaginal intraepithelial neoplasia

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Summary. The effectiveness of 5-fluorouracil (Efudix) in the treatment of vaginal intraepithelial neoplasia was assessed in 14 patients diagnosed with the condition between January 1980 and December 1982. All patients received a standard dose of 2·5 g 5-fluorouracil cream once weekly for at least 10 consecutive weeks; mean duration of treatment was 12 weeks (range 10–20 weeks). The vaginal lesion was associated with a major dysplastic lesion of the cervix in all patients. The duration of follow-up ranged from 4 to 42 months (mean 15 months). Thirteen patients had complete resolution both colposcopically and cytologically. One patient still had colposcopic evidence of intraepithelial neoplasia (aceto-white epithelium) but a vaginal smear has been negative. This patient has since been lost to follow-up. We conclude that in the regimen described 5-fluorouracil is an effective treatment for vaginal intraepithelial neoplasia.

In a small percentage of patients (3–5%) the original squamocolumnar junction is situated caudal to the vaginal fornix (Pixley 1976). Metaplastic epithelium occurring on the vaginal transformation zone is subject to similar dysplastic change as cervical transformation zone epithelium. The incidence of the vaginal intraepithelial carcinoma is estimated to be about 0·4% of all genital tract malignancies (Calgar *et al.* 1981).

The treatment of these vaginal lesions has ranged from radium implants to total or partial vaginectomy (Gallup & Morley 1975). Cryosurgery has been used (Adduci 1972) but good application of the cryoprobe to what is frequently an extensive and occasionally a multifocal lesion is not always practical. Laser therapy has the obvious advantage of accuracy but requires a general anaesthetic and carries the potential risk of inflicting bladder or rectal damage. The use of 5-fluorouracil in the treatment of vaginal carcinoma *in situ* was first described by Bowen-Simpkins & Hull (1975). Since then various treatment regimens have been described. Piver *et al.* (1979) used a 20% 5-fluorouracil cream, and most treatment programmes involve daily application over 5–7 days, repeated at weekly intervals for a number of treatment courses. Stokes *et al.* (1980) described a new treatment regimen for vaginal intraepithelial neoplasia. They reported on the successful use of 2·5 g of 5% 5-fluorouracil cream given weekly for 10 weeks in a case of vaginal intraepithelial neoplasia with minimal side-effects.

The principal advantage of 5-fluorouracil is the preservation of normal vaginal function both during and following treatment and the ease of application as an out-patient has obvious merit. The main disadvantage is the associated vaginal discharge, stinging and temporary superficial dyspareunia which occurs. Many of these disadvantages can be minimized by using a single weekly insertion of 2·5 g of 5% 5-fluorouracil cream as described by Stokes *et al.* (1980). Patients are advised to abstain from intercourse for 24 h following application of the cream in order to avoid penile irritation. We have used this regimen since 1980 and assess its effectiveness in this paper.

Patients and methods

An analysis of the case notes of all patients attending the colposcopy clinic in the Leicester Royal Infirmary between January 1980 and December 1982 was undertaken to identify those patients with intraepithelial vaginal neoplasia.

Patients were originally referred with abnormal cervical cytology and were subsequently found to have vaginal intraepithelial neoplasia. The vaginal lesions were unifocal and very extensive in all cases. Cervical and vaginal punch biopsies were taken in the majority of patients to establish the severity of the lesion. Treatment was with 2·5 g of 5% 5-fluorouracil cream, using a standard vaginal applicator, once a week at night and continued for 10 weeks. Occasionally a second course of 10 weeks was prescribed where the initial course failed to eradicate the lesion.

Patients were seen 4 months after treatment and every 6 months thereafter. Colposcopic examination and vaginal cytology were performed at each visit Any area suggestive on colposcopy of vaginal intraepithelial neoplasia was biopsied. Individual patients are described under results.

Results

Between January 1980 and December 1982, 632 new patients with dyskaryotic smears were seen at the colposcopy clinic in the Leicester Royal Infirmary. There were 14 patients with vaginal intraepithelial neoplasia, an incidence of 2·2% in this group.

The average age of patients was 34·5 years and six were nulliparous. Table 1 shows the age, parity and degree of cytological abnormality at the time of presentation.

Nine patients had cervical intraepithelial neoplasia (CIN) diagnosed on punch biopsy of the cervix, six of these had CIN III and three had CIN II. One diagnosis of CIN III was made on cone biopsy and four patients had CIN III at the time of abdominal hysterectomy, three of these previously had CIN III incompletely excised on cone biopsy. Seven patients had carcinoma *in situ* of the vagina, two had severe dysplasia and one patient had mild dysplasia. The remaining four patients did not have vaginal biopsies but had definite colposcopic evidence of severe dysplasia (aceto-white epithelium, mosaicism and punctation).

Twelve patients, treated for 10 weeks with 2·5 g of 5% 5-fluorouracil cream, showed complete resolution of the vaginal lesion. Two patients had persistent evidence of vaginal intraepithelial neoplasia, and abnormal cytology after treatment required a further 10 weeks treatment. One of these patients still had colposcopic evidence of vaginal intraepithelial neoplasia and a smear consistent with carcinoma *in situ* 11 months after initial treatment and was treated with laser destruction under a general anaesthetic, subsequent follow-up at 4 months has been negative.

Table 1. Degree of cervical dysplasia associated with vaginal intraepithelial neoplasia

Patient	Age (years)	Parity	Cytology	Cervical biopsy
1	21	0	Moderate dyskaryosis	CIN III
2	21	0	Moderate dyskaryosis	CIN II
3	22	0	Suggestive of carcinoma *in situ*	CIN III
4	24	2	Suggestive of carcinoma *in situ*	CIN II
5	25	0	Suggestive of carcinoma *in situ*	CIN III
6	28	3	Suggestive of carcinoma *in situ*	CIN III
7	31	3	Suggestive of carcinoma *in situ*	CIN III
8	35	1	Suggestive of carcinoma *in situ*	CIN III
9	36	0	Suggestive of carcinoma *in situ*	CIN III—cone & TAH
10	36	0	Suggestive of carcinoma *in situ*	CIN III
11	48	5	Moderate dyskaryosis	CIN III—cone & TAH
12	48	5	Suggestive of carcinoma *in situ*	CIN III—cone & TAH
13	50	2	Suggestive of carcinoma *in situ*	CIN III—cone
14	58	2	Suggestive of carcinoma *in situ*	CIN III—cone & TAH

All patients have now had a negative follow-up examination. The duration of follow-up has varied from 4 to 42 months with a mean duration of 15 months. One patient has had seven negative follow-up examinations; one patient has had six; two patients have had four; four patients have had three; two patients have had two and three patients have had a single negative follow-up examination One patient was lost to follow-up while she still had an aceto-white patch on her vagina, although a smear from this area was negative. The details of all 14 patients are summarized in Table 2. Twelve patients have been successfully treated with 5-fluorouracil, one patient failed to respond to a second course of treatment and was successfully treated with the laser and one patient was lost to follow-up The cervical lesion was treated with cryosurgery in four patients, laser in one, cone biopsy in one, total abdominal hysterectomy in four and no treatment was required apart from 5-fluorouracil in four patients. Side-effects during treatment were minimal and confined to a sensation of vaginal burning and mild dyspareunia. No patient had to interrupt treatment as a result of side-effects. Desquamation of the abnormal epithelium was noted at the time of first follow-up at 4 months but there was no desquamation of normal epithelium.

Discussion

The occurrence of vaginal intraepithelial neoplasia was first described in the English literature

Table 2. Details of treatment and follow-up of 14 patients with vaginal intraepithelial neoplasia

Patient	Vaginal biopsy	Therapy	Follow-up	Therapy	Follow-up	Therapy	Follow-up
1	No biopsy	Efudix	Negative×3	—	—	—	—
2	Moderate dysplasia	Cryo-surgery to cervix	Negative smear/ aceto-white vaginal epithelium	Efudix	Negative smear but still aceto-white changes on vagina	DNA	—
3	No biopsy	Efudix	—	Cryo-surgery to cervix	Negative×3	—	—
4	No biopsy	Efudix	CIN III of cervix	Cryo-surgery to cervix	Negative×1, dyskaryotic vaginal smear on 2nd follow-up	Efudix	Negative×1
5	Mild dysplasia	Cryo-surgery to cervix	Dyskaryotic smear, aceto-white vaginal epithelium	Efudix	Negative×2	—	—
6	Ca *in situ*	Efudix	Negative×7	—	—	—	—
7	No biopsy	Efudix	Negative×4	—	—	—	—
8	Ca *in situ*	Efudix	Negative×2	—	—	—	—
9	Ca *in situ*	Efudix	Vaginal biopsy, Ca *in situ*	Efudix	Dyskaryotic smear/aceto-white vaginal changes	Laser to vagina	Negative×3
10	Ca *in situ*	Efudix	Vagina healed CIN III of cervix	Laser to cervix	Negative×3	—	—
11	Moderate dysplasia	Efudix	Negative×1	—	—	—	—
12	Ca *in situ*	Efudix	Negative×1	—	—	—	—
13	Ca *in situ*	Efudix	Negative×4	—	—	—	—
14	Ca *in situ*	Efudix	Negative×6	—	—	—	—

by Scokel *et al.* (1961). Since then a number of reports have appeared (Graham & Meigs 1962; Hull *et al.* 1977) most of which confirm an association with malignant or premalignant lesions of either the cervix or vulva and indicate the unstable nature of these epithelial surfaces. Ballon *et al.* (1979) in a study of 12 patients with vaginal intraepithelial neoplasia quoted a mean age of 44 years. In our study the mean age was 34·5 years and six patients were in their twenties. This is much more in keeping with the known natural history of cervical neoplasia. As invasive squamous carcinoma of vagina generally occurs in the 50–65 year age group it would appear from the early age at which we are now diagnosing vaginal intraepithelial neoplasia that the mean age for invasive squamous carcinoma of the vagina may yet show the same fall as has been seen for early cervical cancer (MacGregor 1981).

It has been stated (Ballon *et al.* 1979) that no specific area of the vaginal epithelium is particularly susceptible to dysplastic change and that the lesions are frequently multifocal. This is not our experience and in all our patients the lesion was confined to the upper third of the vagina and comprised a single large area of abnormality; all were associated with a premalignant lesion of the cervix. There were no associated vulval lesions but this may have been overlooked as no specific effort was made to screen the vulva.

Of the 12 patients described by Ballon *et al.* (1979) three had recurrences, but it is not made clear which patients had recurrence and it is tempting to speculate that they may have been three of the six patients with vaginal carcinoma *in situ*. In a prospective study of 27 patients with vaginal intraepithelial neoplasia, Calgar *et al.* (1981) used 5 g of 5% cream applied daily for 5–10 days, repeated at 2-week intervals and three patients had recurrences at 3, 9 and 11 months. However, in this group only five patients had dysplasia amounting to carcinoma *in situ* and again it is not made clear which patients had recurrences. Piver *et al.* (1979) used a 20% 5-fluorouracil cream and reported two treatment failures out of a total of eight patients and Woodruff *et al.* (1975) reported one 'treatment failure' in a patient with a hyperkeratotic lesion and speculated that poor application of the cream to the underlying dysplastic lesion was responsible for the failure.

In our study seven patients had vaginal carcinoma *in situ* and two patients had moderate dysplasia of the vaginal epithelium and one patient had mild dysplasia. There were two initial treatment failures one of which was successfully treated by a second course of 5% 5-fluorouracil and one by laser vaporization. In conclusion it would appear that a 10-week course of 2·5 g of 5% 5-fluorouracil cream inserted once weekly at night and occasionally repeated for a second course is an effective treatment for eradicating vaginal intraepithelial carcinoma and is almost completely free of side-effects.

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Successful treatment of fetal bladder obstruction *in utero*. Case report

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Case report

The patient was 28 years of age, gravida 2 para 1, who had given birth to a healthy boy 4 years before She was admitted to the hospital at week 27 because of suspected amniotic fluid loss and irregular but painful uterine contractions. No previous ultrasound examination had been done. An ultrasound examination revealed no amniotic fluid The fetus was in breech presentation. The fetal biparietal diameter of 66 mm was small-for-dates. Bilateral hydronephrosis was seen and the bladder was dilated and thick-walled. Otherwise the fetus seemed normally developed. No ascites was present. The placenta was posteriorly located The male sex of the fetus was confirmed in a later ultrasonogram. Medication with ritodrine, 10 mg five times daily, was initiated with betamethasone, 6 mg intramuscularly, also being administered on two subsequent days. After explanation of the situation the mother agreed to a trial of intrauterine treatment. An external cephalic version was performed to improve the accessibility of the fetal bladder. This was difficult because there was no amniotic fluid. The bladder was then punctured with a spinal needle under ultrasonic control using Toshiba Sonolayer real-time apparatus and a 3-MHz puncture transducer. A 30-ml volume of clear yellowish fluid was removed, this contained 4·4 mmol/l of potassium, 116 mmol/l of sodium, 145 μmol/l of creatinine, 0·93 g/l of proteins and had an osmolality of 256 mosmol/l, a small amount of urine remained in the bladder. The hydronephrosis was only slightly relieved and the bladder filled again after 2 days. As the accumulation of fluid was equally rapid after a second puncture, an attempt at permanent drainage was decided on at 29 weeks.

The draining of the bladder was accomplished as follows. Under local anesthesia an 8-cm-long subclavian puncture cannula with an inner steel stylet (Cavafix, Braun, Melsungen, W. Germany, Fig. 1) was introduced into the bladder with ultrasound guidance. Side holes were cut in the vein catheter at its distal end and 20 cm proximally. The stylet of the cannula was removed and 15 cm of the catheter was introduced into the bladder. The catheter was cut 25 cm from its tip. The cannula was retracted until its tip could be slipped upwards along the surface of the fetal abdomen. The rest of the catheter was pushed by its proximal half into the space between the fetal abdomen and the amniotic membrane. No extra tocolysis was used during the procedure Slight vaginal bleeding but no contractions occurred during the next few days. During the following weeks the fetal bladder remained empty and the hydronephrosis was relieved but the pelvis of the left kidney remained somewhat dilated while the right kidney appeared normal. Amniotic fluid accumulated and the fetal biparietal diameter grew along a low normal curve. An amniocentesis, at 37 weeks revealed an amniotic fluid L/S ratio of 3·5 wth positive phosphatidylglycerol, and a creatinine concentration of 91 μmol/l.

The patient went into a spontaneous labour at 38 weeks. The delivery was uneventful and a male infant weighing 3200 g was born with Apgar scores of 9 at both 1 and 5 min At birth the catheter was draining urine and emerged from a point anterior to the left anterior superior iliac spine.

A cystography performed immediately after birth through the catheter revealed a typical posterior urethral valve. An ultrasonogram and urography revealed a small non-secretory right kidney and a dilated left renal pelvis. An external ureterostomy was made on the left side at the age of 1 week, resulting in the disappearance of the pelvic dilatation. Dihydralazine and diuretics were necessary to control the child's high

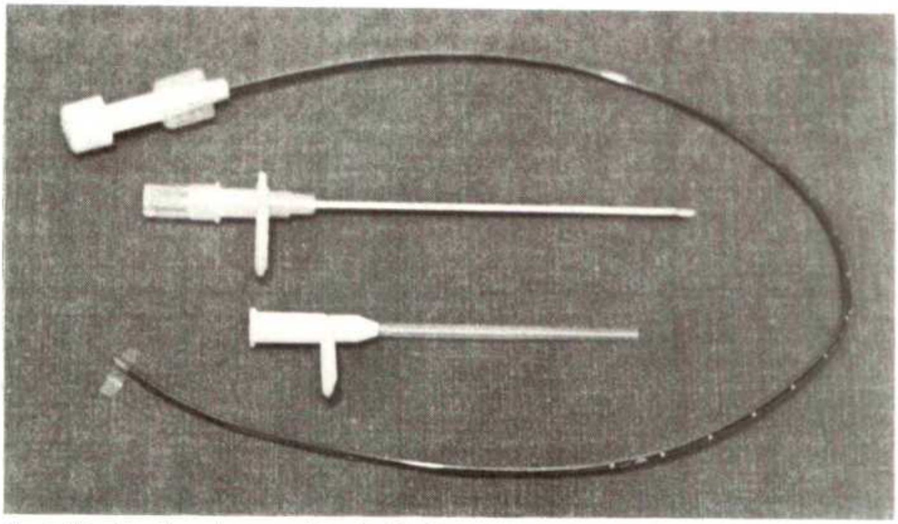

Fig. 1. The Cavafix catheter used for the bladder draining. The plastic cannula and its puncture stylet and the catheter with centimeter markings are separated.

blood pressure until the right kidney was removed at the age of 2 months; thereafter the medication was stopped. The histological investigation of the removed kidney revealed renal dysplasia: a thinned renal cortex with a few hyperplastic glomeruli and tubuli surrounded by fibrosis. In the medulla there were some rudimentary collecting ducts and hyalinoid fibrosis.

The resection of the urethral valve, that completely occludes the urethra, has proved to be technically difficult and the final correction is now planned at the age of 20 months.

Discussion

Severe fetal urinary obstruction, which produces oligohydramnios, fetal hydronephrosis, distended bladder and eventual ascites usually leads to fetal or neonatal death due to underdeveloped lungs (Harrison *et al.* 1981). Furthermore, oligohydramnios leads to flexion contractures and Potter-type facies. Urinary tract dilatation causes renal failure and abdominal muscle deficiency (Harrison *et al.* 1981). As such a severe congenital malformation can be readily diagnosed by ultrasound (Chinn & Filly 1982), there is considerable interest in developing methods for prenatal treatment (Berkowitz *et al.* 1982).

The diagnosis of fetal urinary obstruction with real-time ultrasound equipment is straightforward, and the level of the obstruction and renal function can be determined according to the principles presented by Harrison *et al.* (1981). In our patient proper renal function was ascertained by the rapid filling of the fetal bladder after puncture. We think that this is a prerequisite for attempts at intrauterine treatment of the obstruction, since renal dysplasia is often associated with urinary obstruction (Chinn & Filly 1982; Berkowitz *et al.* 1982). The dysplastic changes may sometimes occur too early in gestation to be influenced by intrauterine procedures (Gonzales 1983).

The prognosis of a fetus with bilateral hydronephrosis and oligohydramnion is grim and justifies efforts of intrauterine catheter placement. Respiratory difficulty due to pulmonary hypoplasia is the immediate postpartum danger (Harrison *et al.* 1981; Berkowitz *et al.* 1982). The accumulation of amniotic fluid allows proper pulmonary development and is most probably the main factor determining the prognosis of the fetus. This was the experience of Golbus *et al.* (1982), in a patient where the normal amniotic fluid of a healthy twin may have prevented compression of the affected twin's thorax as respiratory difficulties did not occur. Such difficulties have occurred when the intrauterine treatment has failed to produce amniotic fluid (Berkowitz *et al.* 1982; Harrison *et al.* 1982).

For postnatal treatment Kruger *et al.* (1980) presented data to suggest that babies with urethral valves will have improved long-term growth and renal function when managed initially with urinary diversion as compared with simple valve resection.

In patients with non-existent amniotic fluid, dilatation of the amniotic cavity with saline (Berkowitz *et al.* 1982) or intrauterine surgery (Harrison *et al.* 1982) have been found necessary. The technique described here was successful in such circumstances and manipulation was possible, although difficult, to place the fetus into the optimal position for catheter placement. Thus the first attempt to relieve bladder obstruction *in utero* can always be placement of a permanent draining tube.

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Recurrence of Cushing's disease in pregnancy. Case report

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Case report

The patient was 28 years old and nulliparous when she presented in 1978. In the preceding 3 years she had noticed weight gain, increasing facial hirsutism, a tendency to bruise and recurrent depression. The clinical features were characteristic of Cushing's syndrome and the diagnosis was confirmed by the demonstration of an absent diurnal rhythm of serum cortisol, an elevated urinary free cortisol and a blunted serum cortisol response to insulin-induced hypoglycaemia. That the patient's condition was pituitary-dependent (i.e. Cushing's disease) was demonstrated by finding suppression of serum and urinary cortisol by 2 mg dexamethasone 6-hourly for 48 h, detectable ACTH levels within the normal range and bilateral adrenal uptake of isotope during a selenocholesterol scan. Trans-sphenoidal microsurgery was undertaken in February 1979 and a 4-mm tumour which seemed to be well demarcated from surrounding tissue was removed. Conventional histology demonstrated a basophil adenoma and biopsies from the tissue surrounding the tumour appeared normal. Immunoperoxidase staining (McNicol 1981) confirmed that the adenoma consisted of ACTH-secreting cells but showed that the surrounding tissue also contained small clusters of ACTH-secreting cells, a pattern consistent with nodular hyperplasia rather than a simple adenoma.

Postoperatively her serum cortisol was low and failed to respond to insulin-induced hypoglycaemia, but 4 months later her hypothalamic–pituitary–adrenocortical function had returned to normal. Cushingoid features gradually resolved but she remained prone to bouts of depression.

Having remained in clinical and biochemical remission for 30 months, she presented in August, 1981 with a threatened abortion at 9 weeks gestation without any clinical features of Cushing's syndrome. However, routine screening demonstrated hypokalaemia (serum potassium 2·2 mmol/l, normal 3·5–5·0 mmol/l) and subsequent testing showed marked elevation of serum and urinary cortisols (see Fig. 1) with high plasma ACTH values (70–135 ng/l; normal range <80 ng/l). Detailed investigation and further treatment other than potassium supplementation were avoided as they might have further jeopardized fetal and maternal well-being.

As pregnancy advanced the patient became overtly and progressively Cushingoid (Fig. 2) despite gradual reduction in her serum and urinary cortisol levels (Fig. 1). She experienced increasing ankle oedema but remained normotensive throughout pregnancy with normal glucose tolerance. Urinary oestrogen levels remained at a low level through pregnancy, an observation compatible with the known suppressive action of glucocorticoids on fetoplacental steroidogenesis (Oakey 1970). Human placental lactogen level rose normally throughout the course of pregnancy. At 34 weeks she went into spontaneous breech labour and underwent an uneventful caesarean section under epidural anaesthesia. A healthy male infant, weighing 2·1 kg was delivered (Apgar scores of 3, 7 and 10 at 1, 5 and 10 min respectively) and showed no clinical or biochemical evidence of adrenal insuf-

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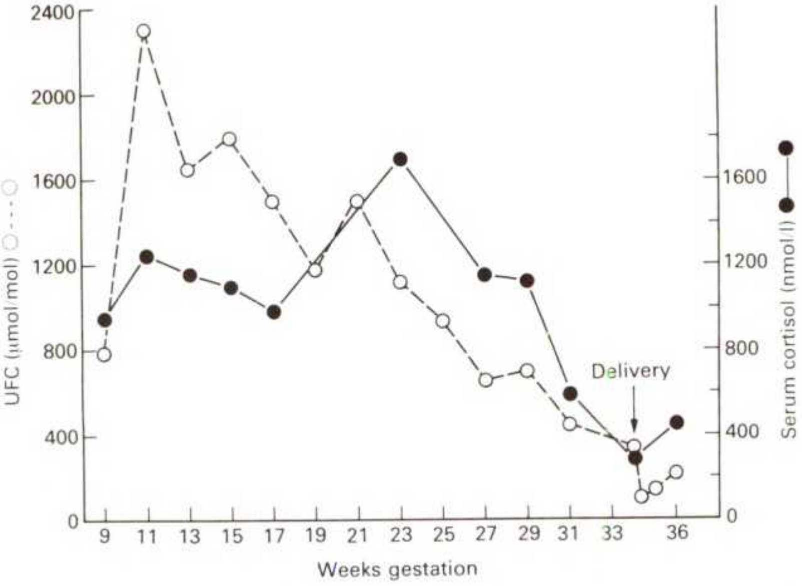

Fig. 1. Urinary free cortisol (UFC) and serum cortisol through pregnancy. Normal ranges 5–40 μmol/mol and 280–720 nmol/l respectively.

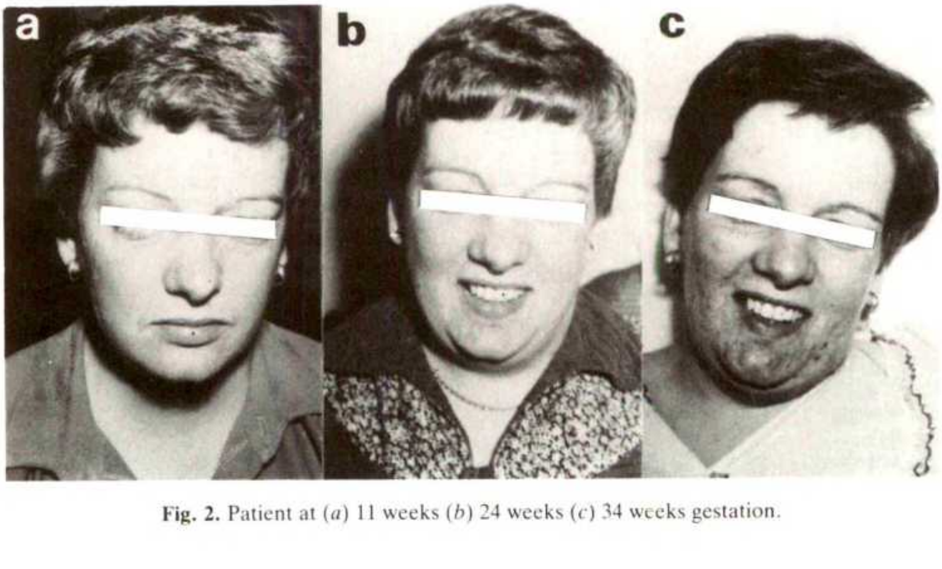

Fig. 2. Patient at (*a*) 11 weeks (*b*) 24 weeks (*c*) 34 weeks gestation.

ficiency. Postpartum wound healing remained a problem until cortisol levels were controlled with metyrapone.

After delivery and before starting metyrapone, dexamethasone, 2 mg 6-hourly for 48 h, suppressed serum and urinary cortisols. Subsequent immunoperoxidase staining of the placenta failed to reveal any ACTH secreting tissues. Pituitary tomography did not show evidence of enlargement of the gland. Because hypokalaemia had been the presenting feature in early pregnancy, it was considered necessary to search for an ectopic source of ACTH as this often presents with an electrolyte disturbance. Selective sampling of the venous effluent of the organs most often implicated as a source of ACTH revealed that the peak central:peripheral ratio for plasma ACTH was 2·2:1·0 in the right internal jugular vein suggesting a pituitary source of ACTH. Intrathoracic tumours, such as thymic or bronchial carcinoids, are commonly implicated in the ectopic ACTH syndrome, but a CT scan of the thorax was normal. Four months postpartum she underwent bilateral adrenalectomy followed by pituitary irradiation. She went into remission and has remained well.

Discussion

Patients with active Cushing's syndrome rarely become pregnant. A review of the literature up to 1982 revealed 34 pregnancies in 30 untreated patients (Gormley *et al.* 1982). In 10 of these the condition was pituitary-dependent; 16 had adrenal tumours and the underlying pathology was uncertain in the remaining four. Impairment of fertility is probably caused by corticosteroid suppression of gonadotrophin releasing hormone induced gonadotrophin release (Boccuzzi *et al.* 1975). Not only is pregnancy rare, but there is a high incidence of fetal loss.

Advances in neurosurgical techniques, in particular the use of the operating microscope, have allowed safe access to the pituitary gland by the trans-sphenoidal route with accurate identification and selective removal of the abnormal part of the gland. Trans-sphenoidal microsurgery is considered by many to be the current treatment of choice for Cushing's disease (Gold 1979).

This case documents the recurrence of Cushing's disease during pregnancy following apparently successful removal of an ACTH-secreting pituitary adenoma. Although only isolated instances of recurrence following pituitary surgery have been previously reported (Pont & Gutierrez-Hartman 1979; Bigos *et al.* 1980), further examples are likely to follow as the operation increases in popularity and follow-up lengthens (Burch 1983). Immunocytochemical techniques have demonstrated, as in this case, that some patients with Cushing's disease show nodular hyperplasia (McNicol 1981) rather than an isolated adenoma accompanied by a reduction in the number of ACTH cells in surrounding tissue. It has been proposed that the former pattern is due to hypothalamic overstimulation rather than primary pituitary pathology (Lamberts *et al.* 1980) and it would follow that this group of patients might recur more frequently following apparently successful surgery.

Plasma and urinary free cortisol are known to increase during normal pregnancy, in the latter case after reaching values two to three times greater than the non-pregnant upper limit of normal (Van der Spuy & Jacobs 1984). In our patient, however, the very high levels of plasma and urinary free cortisol seen in early pregnancy gradually fell towards levels which would have been considered physiological in a normal pregnancy. The fulminating nature of our patient's second presentation suggests that the recurrence may have been triggered or exacerbated by the onset of pregnancy. Cushing's disease has been known to remit spontaneously during pregnancy (Lee & Rapoport 1972) so clearly it does not always have an adverse effect on the progress of the disease.

Hypokalaemia in Cushing's syndrome may signal the presence of an ectopic tumour producing ACTH, but there is no evidence for such a tumour in our patient. Moreover, some previous cases of Cushing's syndrome in pregnancy (Parra & Cruz-Krohn 1966; Wieland *et al.* 1971) have also had this feature and it seems possible that hormonal changes of pregnancy may interact with increased corticosteroid secretion to produce this effect.

Low urinary oestrogen levels are known to occur in pregnant patients on synthetic corticosteroids (Oakey 1970). This is thought to occur because the consequent inhibition of fetal ACTH production leads to suppression of fetoplacental function. It is surprising, however, that infants of mothers with Cushing's syndrome do not usually develop adrenal insufficiency. Only a single such case has been recorded) Kreines & De Vaux 1971) although adrenal atrophy has been found in several stillborn infants of these mothers (Kreines *et al.* 1964). The infant of our patient remained well apart from mild neonatal jaundice and his serum cortisol levels measured within 24 h of delivery were normal. The neonatal pituitary-adrenocortical axis seems to be able to recover rapidly from suppression by corticosteroids.

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SHORT COMMUNICATIONS

The sex ratio of infants born after hormonal induction of ovulation

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If the sex of human offspring were partially controlled by the mother's gonadotrophin level at the time of conception, then much of the established variation at birth of the human sex ratio would be explained (James 1980*a*). An examination of the available evidence suggests that, if such a hypothesis were true, high gonadotrophin levels would favour female conceptions. Preg-

Table 1. The sexes at birth following induction of ovulation by gonadotrophin and/or clomiphene

Source	Singletons		Twins		Higher multiples		All	
	M	F	M	F	M	F	M	F
Aiken (1969)					3	4	3	4
Atlay & Pennington (1971)					2	1	2	1
Barrat & Leger (1979)							179	238
F. J. Beernink (personal communication, 1984)							291	359
Berg *et al.* (1983)					2	7	2	7
J. B. Brown (personal communication, 1981)	63	67	33	23	8	14	104	104
Burnell (1974)					4	3	4	3
S Byrne (personal communication, 1980)							40	41
Chapman & Malvern (1982)					2	2	2	2
Cholst *et al.* (1981)	35	32	22	20	34	40	91	92
Correy *et al* (1982)							73	59
Eckstein & David (1978)					4	2	4	2
Garrett *et al.* (1976)					5	4	5	4
Giovannucci-Uzielli *et al* (1981)					4	2	4	2
Granat (cited by Schenker *et al.* 1981)					4	0	4	0
James (1980*b*)	57	76	32	55	49	54	257	333
Karafiol *et al.* (1982)					1	2	1	2
Leysen *et al.* (1984)			2	0			2	0
Liggins & Ibertson (1966)					1	4	1	4
G M. Masson (personal communication, 1982)	56	52	8	10	3	6	67	68
Mobius & Carol (1978)					4	4	4	4
Muechler *et al* (1981)	0	1			0	3	0	4
Neuwirth et al (1965)					1	3	1	3
Turksoy *et al* (1967)					2	5	2	5
Varga *et al.* (1974)					2	3	2	3
Wu *et al.* (1983)					4	0	4	0
Zimmermann *et al.* (1982)	29	30	23	21	6	6	58	57
Total	240	258	120	129	145	169	1207	1401
Sex ratio	92		92		85		85	

The numbers in respect of Barrat & Leger (1979) are the sums of the numbers in their Tables II, IV and VI. The numbers in respect of Cholst *et al* (1981) have been augmented by data from Dr Jewelewicz (personal communication, 1981). The quadruplets reported by Atlay & Pennington (1971) contained a monoamniotic twin pair of boys. So the number of male zygotes was presumably two, not three. The data were tested for heterogeneity. In doing so, the 18 smaller samples were ignored as providing practically no information. The remaining nine largest samples yielded a χ^2 of 12·3 with 8 d.f. ($0{\cdot}1<P<0{\cdot}2$). So there is no good evidence for heterogeneity here.

nancies following the induction of ovulation by gonadotrophin or clomiphene should therefore contain an excess of female infants. Preliminary evidence has been cited in support of this inference (James 1980*b*), but the point has recently been questioned (Ben-Rafael *et al.* 1984). Accordingly I present here all the data I have been able to collect. They suggest that there is indeed a small but highly significant excess of female births following the induction of ovulation by gonadotrophin or clomiphene.

It seems possible that artificial insemination has an independent effect on the sex of offspring, perhaps also mediated by hormone levels (James 1984), so attention here will be confined to the sexes of infants conceived after hormonal induction of ovulation and natural insemination.

Table 1 summarizes the published data, together with further data from workers whose papers suggested that they might have relevant unpublished material.

The overall sex ratio (number of males per 100 females) in these data, 85, is significantly different from the normal human sex ratio at birth, which is about 106 (Bulmer 1970) ($\chi_1^2 = 27{\cdot}4$, $P<2\times10^{-7}$). Thus there can be little doubt that there is an excess of girls, small but significant, following hormonal induction of ovulation. Whether this is due to the high levels of gonadotrophin is not clear, but at least the inference drawn from the hypothesis *does* seem to be true.

Acknowledgments

I am grateful to Dr F. J. Beernink (Berkeley, California), Professor J. B. Brown (University of Melbourne), Sister S. Byrne (Women's Hospital, Sydney, Australia), Mr G. M. Masson (University of Southampton) and Dr R. Jewelewicz (Columbia University) for providing me with data.

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BOOK REVIEWS

Clinical Pharmacology in Pregnancy. Rational Pharmacotherapy edited by Helmut P. Kuemmerle & Klaus Brendel. Georg Thieme Verlag, Stuttgart, 1984, 286 pages with figures and tables, DM 178

Clinical pharmacology and the problems of rational therapy in pregnancy are 'en vogue'. Books and reviews on these topics seem to be popping out as fast as mushrooms—alas, often conveying little more than already well-known facts. Yet, the vast subject is still insufficiently explored; in fact we are just beginning to understand some of its complexities. What news then does this contribution bring? The book is divided in two parts. The first deals with the fundamentals of drug therapy, the second with applied clinical pharmacology in pregnancy. The subtitles cover almost every relevant aspect, including the ethical, legal and judicial. Inevitably, in 59 chapters written by 29 different authors there is a good deal of overlapping and repetition. Moreover, the shortness of the chapters does not usually allow comprehensive treatment of the different subjects. Nevertheless, there are some outstanding contributions—either for their didactive value and clarity or their originality. For example there is an enlightening account on the fundamentals of human embryogenesis. One chapter gives a good overview on drug metabolism in the fetus; another on transplacental toxicology, where even the effects of derivatives of plants and fungi possibly present in the mixtures used in so-called 'folk medicine' are described. These agents—mostly alkaloids—are known to produce a variety of malformations in animals. There is also a chapter on embryotoxic drugs with a list of examples of dysmorphorgenic agents and their respective molecular mechanisms of action. The chapter on the pharmacology of the pregnant human uterus gives a clear and succinct account on the physiological mediators and therapeutic agents for the control of uterine contractility. There are several (scattered) chapters dealing with the complex pharmacokinetic problems of drug dosage regimens, maternal–fetal drug transfer and passage to milk. A model is given for the estimation of the degree of drug accumulation in the breast-fed infant, based on a few simplifying assumptions and on a series of computer simulations. While such models may appear unpractical to the clinician, it must be realized that they may be valuable tools for the prediction of drug concentration in the maternal–fetal unit and the breast-fed infant. The last part of the book constitutes an appendix with the descriptions (indications and contraindications during pregnancy) of various drugs, drug classes and groups including hormones, 'psychotomimetic' and psychotherapeutic drugs, vitamins and immunological agents. Interestingly, amongst the described antibiotics, erythromycin is listed as contraindicated during pregnancy on the grounds that it should exert some adverse effects on the fetus. The corresponding reference is missing. The book is a typical multi-author production with contributions of varying quality. It does not convey new facts or views, but it certainly gives a good account on the enormous difficulty and complexity of the subject. Moreover, it is undoubtedly of some practical value and should be in the library of any hospital or specialist interested in the matter.

Beatrice Krauer

Essential Reproduction/Second edition by Martin Johnson & Barry Everitt. Blackwell Scientific Publications, Oxford, 1984, 378 pages with figures and tables, £10.80

This integrated approach to the study of mammalian reproduction is written for medical, veterinary and science students. Whilst in all species there are common fundamental points of reproductive events, there are many areas of variation and the details observed among different species have then been emphasized by the use of well-planned tables and figures, rather than prolonged description in the text and destruction of the general emphasis of the specific chapter. The importance of these fundamental differences has been stressed between species since its appropriate extrapolation of reproductive events in other species, which has resulted in the past in the misunderstanding of events as subsequently proven. All the major areas of reproduction are covered from sexual differentiation, regulation of gonadal function, action of steroids, implantation and establishment of placentation, maternal recognition and support of pregnancy, fetal physiology, events associated with parturition, lactation and maternal behaviour. The only area not adequately covered is that of embryonic development, otherwise the book is a very comprehensive review of reproductive physiology. I feel that its title is apt and will indeed become an essential of the basic reading texts for students undertaking a physiology or zoology course. In addition I think it would be of great value for medical students wishing to gain a wider knowledge of reproductive processes, and postgraduates entering into the field of reproductive endocrinology.

R. W. Shaw

Biological Effects of Ultrasound: Mechanisms and Clinical Implications. NCRP Report 74. National Council on Radiation Protection and Measurements, 7910 Woodmont Ave, Bethesda, MD 20814, 1983, 266 pages with figures and tables, US$15.00

The safety of diagnostic ultrasound has attracted the attention of the media in recent months. This report provides all involved in ultrasound with a useful reference on which to base their own assessments of any possible hazard. The report was prepared by an international panel of experts who are contributors to the many facets of the subject. Almost half of the report is concerned with the basic physics of ultrasound fields and the mechanisms of ultrasound and tissue interactions. Clinicians may find this unfamiliar ground but such a basis is necessary for understanding the reviews of publications dealing with the effects of ultrasound. These reviews are of necessity selective but present a fair and reasonably concise acount of the many studies carried out on man, animals, plants and cell lines using a variety of exposure conditions. The problems of extrapolating the results of in-vitro experiments to the clinical situation are highlighted. Despite the lack of known harmful effects in man the report concludes that it is considered prudent for physicians to minimize the ultrasound exposure required to achieve medical objectives. The report identifies the need for further research into the biological effects of ultrasound and the need for the improvement of the specification of exposures used in experiments so that a proper comparison and repetition is possible. It is also suggested that manufacturers should quote the output of their equipment. Finally useful recommendations are made for the education and training of those involved in ultrasound scanning. This comprehensive report is well presented and will be of value to physicists and clinicians alike.

Margaret B. McNay and John E. E. Fleming

Books received some of which will be reviewed at a later date

A Clinician's Guide to Fungal Disease (Infectious Diseases and Antimicrobial Agents Series, Volume 5) by Stephen O. B. Roberts, R. J. Hay & D. W. R. Mackenzie. Marcel Dekker Inc, New York, 1984, 252 pages fully illustrated with figures and tables, $59.00, SWFR 135

Respiratory Distress Syndrome edited by K. O. Raivio, N. Hallman, K. Kouvalainen & I. Valimaki, Academic Press, London, 1984, 421 pages with figures and tables, £32.00

Eating Disorders: The Facts by Suzanne Abraham & Derek Llewellyn-Jones. Oxford University Press, Oxford, 1984, 162 pages with figures and tables, £6.95

Obstetric Analgesia and Anaesthesia Second Edition, (Current Reviews in Obstetrics and Gynaecology No 1) by J. Selwyn Crawford. Churchill Livingstone, Edinburgh, 1984, 169 pages, £9.00

Carbohydrate Metabolism in Pregnancy and the Newborn edited by H. W. Sutherland & J. M. Stowers. Churchill Livingstone, Edinburgh, 1984, 237 pages with figures and tables, £26.00

Coagulation Problems During Pregnancy (Current Reviews in Obstetrics and Gynaecology No 10) by Elizabeth A. Letsky. Churchill Livingstone, Edinburgh, 1984, 137 pages with figures and tables, £9.95

The Pharmacology of the Urinary Tract edited by Marco Caine. Springer-Verlag, Berlin, 1984, 167 pages with figures and tables, £26.00

Immunological Factors in Human Contraception edited by S. Shulman & F. Dondero. Field Educational Italia, Acta Medica, Rome, 1984, 234 pages with figures and tables, £19.20

Clinical Infertility by David W. Keller, Ronald C. Strickler & James C. Warren. Appleton-Century-Crofts, Connecticut, 1984, 278 pages with figures and tables, £28.00, US$33.00

Long-Acting Contraceptive Delivery Systems. Proceedings of an International Workshop on Long-Acting Contraceptive Delivery Systems, 1983 New Orleans, Louisiana, edited by G. I. Zatuchni, A. Goldsmith, J. D. Shelton & J. J. Sciarra. Harper & Row, Philadelphia, 1984, 656 pages with figures and tables, £23.75

The Medical Management of Menopause and Premenopause by Winnifred Berg Cutler & Celso-Ramon Garcia. J. P. Lippincott, Philadelphia, 1984, 275 pages with figures and tables, £26.25

The Apocrine Glands and the Breast by Marshall B. L. Craigmyle. John Wiley & Sons, Chichester, 1984, 82 pages with figures and tables, £24.00

Prenatal Diagnosis and Surgical Treatment of Congenital Malformations Proceedings of the International Medical Congress promoted by the 'Movimento per la Vita Italiano' in collaboration with Facolta di Medicina e Chirugia dell'Universita di Roma e dell Università Cottolica del Sacro Cuore, Roma, Rome 1982 edited by A. Pachi, A. Calisti & G. Astrei. Piccin/Butterworths, Padua, Italy, 1984, 322 pages with figures and tables, £35.00

Sudden Infant Death: Patterns, Puzzles and Problems by Jean Golding, Sylvia Limerick & Aidan Macfarlane. Open Books Ltd, Somerset, 1985, 264 pages with figures and tables, £6.95

Pathology of the Placenta (Contemporary Issues in Surgical Pathology Vol 5) edited by Eugene V. D. K. Perrin. Churchill Livingstone, Edinburgh, 1984, 224 pages with figures and tables, £42.00

Preterm Birth: Causes, Prevention and Management edited by Fritz Fuchs & Phillip G. Stubblefield. Collier Macmillan Limited, West Drayton. 1984, 392 pages with figures and tables, £43.25

Contemporary Obstetrics 293 pages with figures and tables and **Contemporary Gynaecology** 314 pages with figures and tables by Geoffrey Chamberlain. Butterworths, 1984, £18.50 each

Directions to contributors

All papers should be sent to The Editor, *British Journal of Obstetrics and Gynaecology*, 27 Sussex Place, Regent's Park, London NW1 4RG. Papers received are assumed to have been submitted exclusively to the *British Journal of Obstetrics and Gynaecology* and *all* authors must give signed consent to publication in a letter sent with the manuscript. The Editor will decide on the time of publication and retains the usual right to modify the style and length of a contribution; major changes will be agreed with the author(s).

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The summary should contain a factual account of the methods and results in not more than 150 words, rather than a description of the subject of the paper and the opinions of the author(s), brief communications require no summary

Tables and figures

Tables and figures should be separate from the text, with their positions indicated in the text margin. Both are numbered with arabic numerals. Colour illustrations are allowable only in special circumstances and the author will be expected to meet the cost of reproduction.

Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

Figures consist of all material which cannot be set in type, such as photographs, line drawings, etc. Tables are not included in this classification and should not be submitted as photographs Original X-ray films should not be sent—glossy prints must be submitted

Line drawings should be on white board, arranged to conserve space, and should allow for reduction to 65 mm (single column) or 134 mm (double column).

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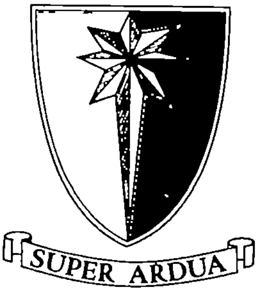
Edited by Frank E. Hytten



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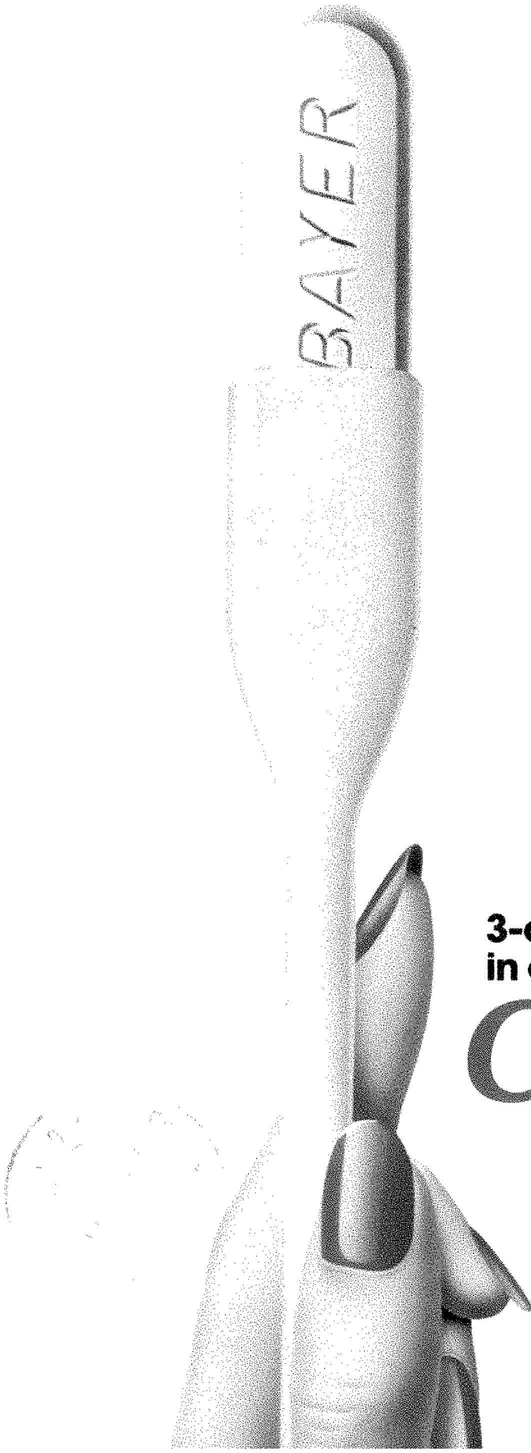

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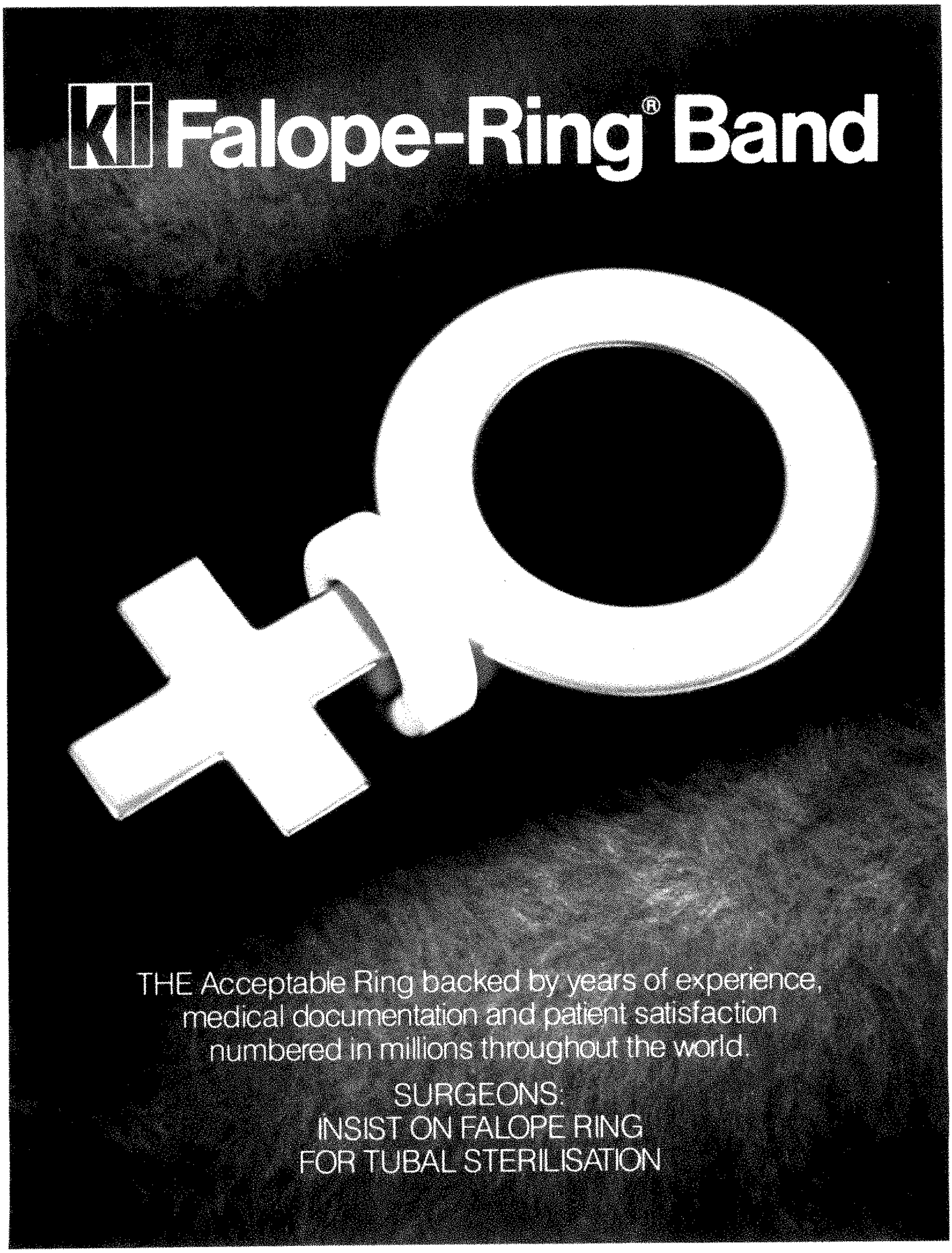

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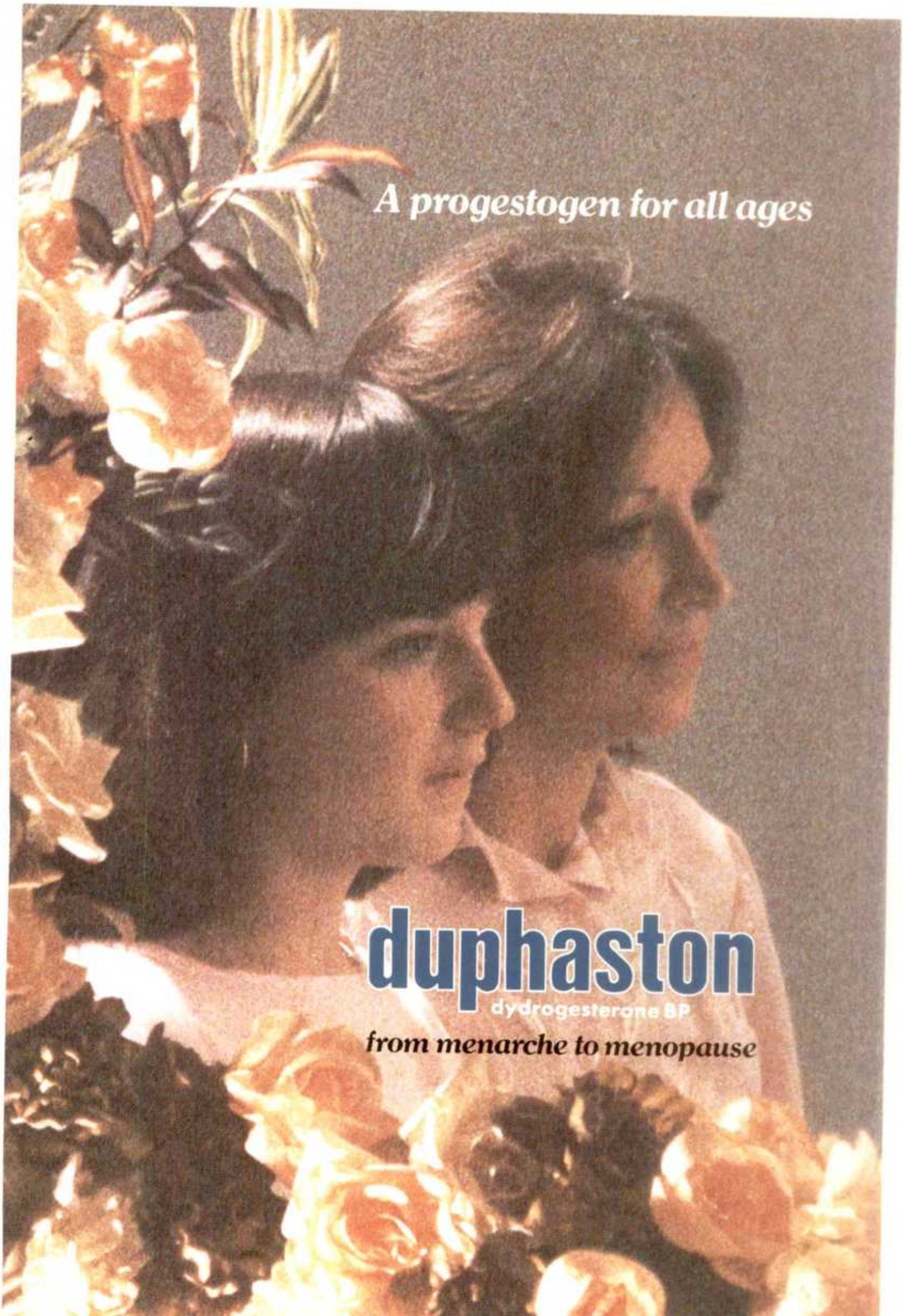

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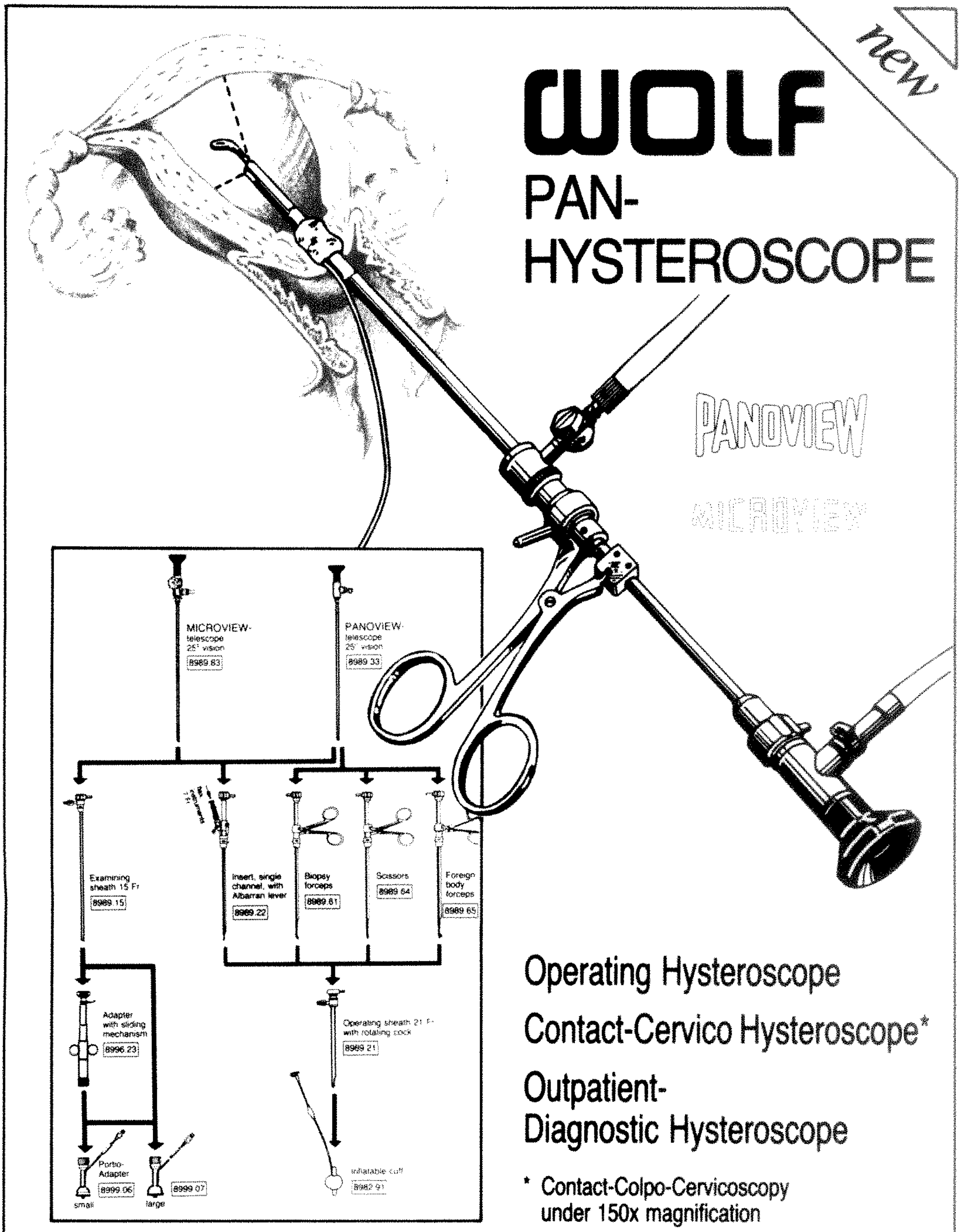
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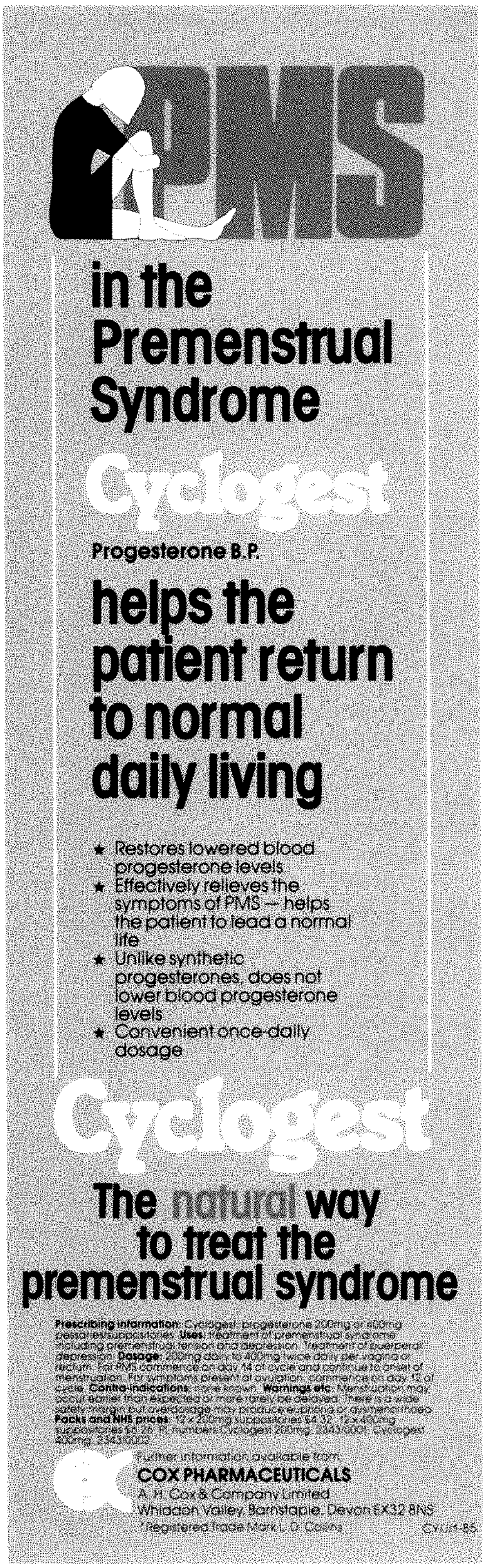

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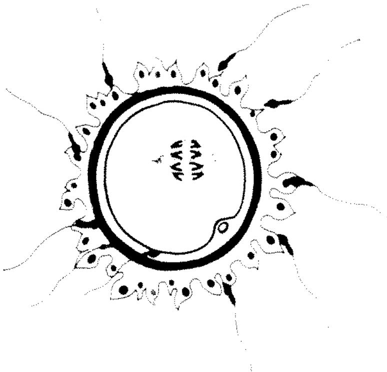

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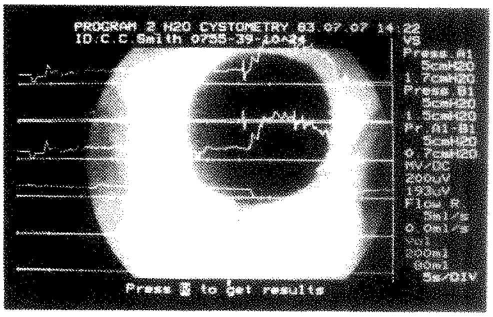
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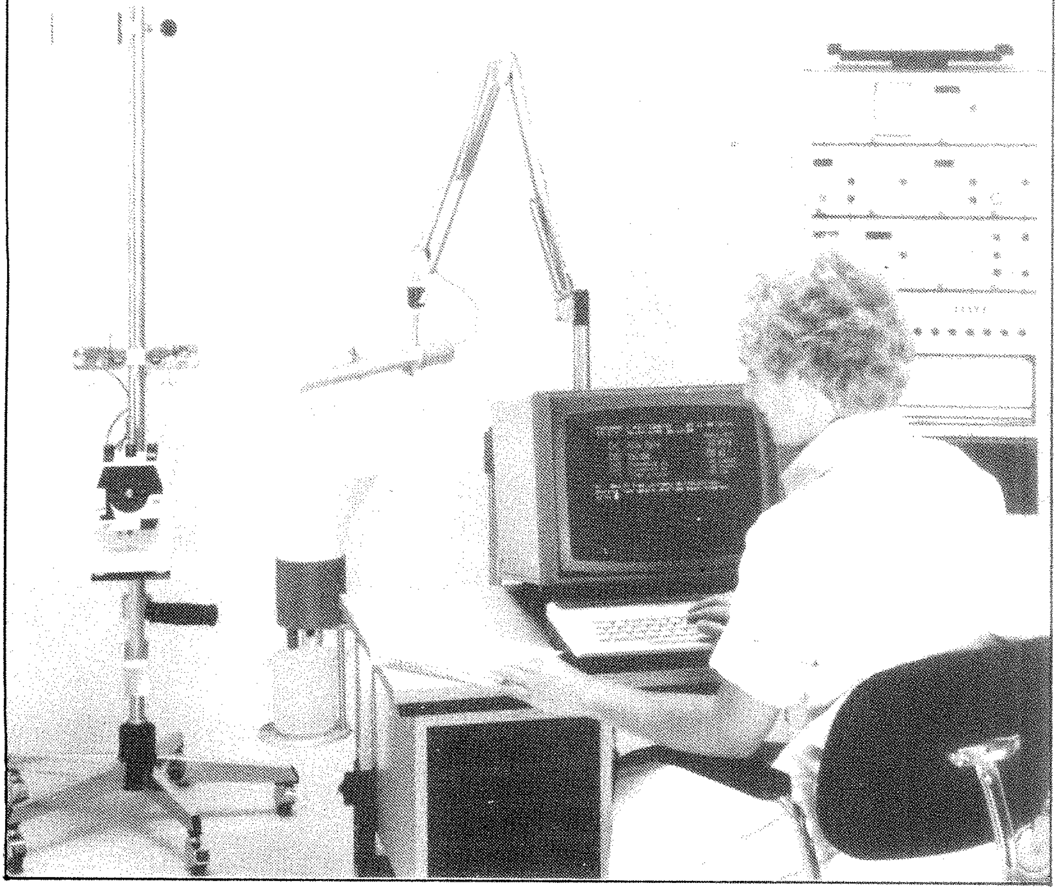

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COMMENTARY

Research on early human embryos from in-vitro fertilization (IVF): the Warnock recommendations

What did the Warnock Report recommend?

The report of the Committee of Inquiry into Human Fertilization and Embryology chaired by Dame Mary Warnock recommended that research on human eggs fertilized *in vitro* should be permitted for up to 14 days after fertilization, whether the eggs had been donated for research purposes or were fertilized as part of a therapeutic programme. Embryos used for research should not be transferred to a uterus. Similar recommendations had previously been made by the Royal College of Obstetricians & Gynaecologists (1983), the British Medical Association (1983) and the Medical Research Council (1982).

The Warnock Committee further recommended that all research projects be approved by a statutory licensing body, and be carried out under the supervision of a named licence holder, under strict controls. Any unauthorized use of an in-vitro embryo would constitute a criminal offence.

What is the human embryo like at this stage?

At this stage of development, the term 'embryo' is a misnomer. The product of the fertilized egg should be termed the *conceptus*. The egg cleaves over the course of a few days to give a clump of a hundred or so cells, and the great majority of these give rise during the course of implantation to the extraembryonic tissues (placenta, yolk sac, amnion) that will provide protection and nourishment to the future embryo. A small group of cells, the embryonic plate, in the centre of the conceptus, remains undifferentiated: within this forms the primitive streak (beginning at 13–14 days after fertilization), which gives rise to yet more extraembryonic tissue (allantois) but also to the embryo proper. It is this 'embryo proper' which will develop into the fetus and thence into the baby. For a more detailed discussion of landmarks in human embryonic development, see McLaren (1984)

Why 14 days?

Up to the end of the implantation stage, there is no way of telling whether the conceptus is going to give rise to one embryo or two, since two primitive streaks can form on a single embryonic plate. This is the latest stage at which monozygotic twinning can take place, and so marks the initiation of *individual* human development If fertilization has been abnormal, the conceptus may give rise only to a tumour, the hydatidiform mole, and not to an embryo at all. It is not until about 15 days after fertilization that the cells of the embryo proper are separated out from the cells of the extraembryonic membranes. No structures such as heart or brain are yet present: the neural tube begins to close at 22–23 days after fertilization, constituting the first beginnings of the central nervous system, though this does not become functional until considerably later in pregnancy. The end of the 14th day was regarded as being just prior to the beginning of individual development *in vivo*, though of course *in vitro* development may take place more slowly.

What research is done on the IVF conceptus?

Most of the research in progress at present is concerned with the alleviation of infertility, including improvements in the efficiency of IVF itself. It should be remembered that we owe the IVF procedures so widely used today to the years of research on in-vitro fertilization of donated eggs carried out by Edwards and Steptoe and their colleagues.

Examples of ongoing infertility research are:

(a) Production of human chorionic gonadotrophin (hCG) by the conceptus. This is thought to be crucial for successful implantation.

Fishel *et al.* (1984) showed that blastocysts from IVF were capable of secreting hCG into the culture medium. Culture conditions that ensure adequate hCG production early in development should increase the IVF pregnancy rate. An understanding of why hCG secretion sometimes fails may also throw light on the high rate of implantation failure in fertile cycles (Edmonds *et al.* 1982).

(b) Low-temperature storage of unfertilized eggs. Successful pregnancies are now being reported from in-vitro fertilized eggs frozen at the 4–8 cell stage. However, storage would raise fewer ethical problems if eggs could be frozen before fertilization rather than after, especially when young unmarried women undergoing cancer therapy wish to store their genetic material for future use Experiments on mice have shown that fertilization and normal development is possible after low-temperature storage of unfertilized eggs, but research on human material will be required to ensure that such a procedure is safe for clinical use, with the thawed-out eggs cleaving normally after IVF

(c) Fertilizing capacity of oligospermic men. It seems that some oligospermic men produce good quality sperm though in very small numbers, and hence could benefit from IVF, while others produre abnormal sperm incapable of supporting normal development. An IVF test system using donated eggs can be used to look for correlations of fertilizing capacity (followed by normal cleavage) with various features of sperm phenotype, such as motility characteristics. If some positive correlation is found, clinicians will be able to advise on appropriate therapy, after a simple examination of the sperm.

Research on new methods of contraception also requires the use of IVF test systems. For example, a steroidal analogue that interferes with oocyte maturation could only be considered for clinical use if it inhibited fertilization entirely, rather than producing abnormal fertilization.

What research could be done?

As well as continuing to advance infertility therapy and contraceptive development, research on the human conceptus could contribute to the prevention of genetic defects. For example, if a few cells could be removed from the preimplantation conceptus and cultured, it might be possible to apply chromosomal (e.g. for Down's syndrome) or molecular (e.g. for thalassaemia) diagnostic methods to check whether the conceptus was affected. If it proved normal, the rest of the conceptus could then be recovered from storage and replaced in the woman. Unlike amniocentesis or chorionic villus biopsy, this method would avoid having to terminate an affected pregnancy; but it will require a considerable amount of research to show that the conceptus is not compromised by taking an 'embryonic biopsy', and that the diagnostic procedures are feasible.

Studies on the timing and conditions of fertilization may also throw light on the causes of some of the chromosomal abnormalities so common in human embryos.

Why not use non-human material?

Any research undertaken on the human conceptus is based on a huge body of earlier animal studies, so that the very scarce resource of human eggs and conceptuses may be used to maximum advantage. The basic techniques of oocyte recovery, in-vitro fertilization and transfer to the uterus were worked out on laboratory and farm animals years before they were attempted in women. Research is like a pyramid: very large numbers of experiments on (for example) mice and rats, or cell cultures (including human); many fewer experiments on primates, if appropriate; and finally a very small number of critical studies on human material. Because of species differences, the last step can never be omitted if a procedure is to be used in clinical practice

Who would benefit from the research?

It has been estimated that a quarter of a million couples in England and Wales have an infertility problem, with male and female infertility about equally prevalent. Advances in contraceptive technology would benefit still more people, and should lead to a reduction in the number of induced abortions (about 125 000 per year) Genetic defects affect about 1% of babies born, i.e. about 70 000 babies per year in the UK; while of the 250 000 spontaneous abortions occurring every year in the UK, more than half have recognizable chromosome abnormalities. These are problems that cause much individual suffering and constitute a heavy social burden, and their alleviation is therefore a matter of some urgency. The contribution to human health and happiness that advances in reproductive medicine can make is immense. Such advances can only come about as a result of research, including research on the human conceptus.

How would research material be obtained?

In the past, any conceptus surplus to therapeutic requirements in an IVF programme has, with the consent of the couple, been available for research ('spare embryos'). Now that many clinics offer freezing as an option, couples prefer to have any surplus stored for their own possible future use, so this source of material is no longer available. In any case, a conceptus deemed 'spare' at the time of replacement is clearly no use for studies of the fertilization process itself. Fortunately, many women undergoing laparoscopic sterilization are willing to donate oocytes for research purposes (Templeton *et al.* 1984) and these are now being used in a variety of projects (e.g. Angell *et al.* 1983).

What status does our society give the early human conceptus?

In couples at risk of pregnancy, more than half the eggs fertilized probably fail to implant (Edmonds *et al.* 1982), say about a million per year in the UK. A further 7 million conceptuses fail to implant because of the presence of an intrauterine contraceptive device. We do not grieve for these conceptuses, nor do we regard them as persons. In a society that tolerates 125 000 induced abortions per year, and does not offer the abortus baptism or Christian burial, it would seem inconsistent for the pre-14-day conceptus to be given absolute protection.

What is the ethical status of research on the early human conceptus?

The early human conceptus is alive, and human, and genetically unique, as also are unfertilized eggs and sperm; but it is not yet a sentient being, nor even an individual. It has the potential to develop into a human person, but only if transferred to a uterus, just as the unfertilized egg has the potential to become a conceptus, but only if fertilized by a sperm. Clearly potential does not in itself confer moral status Professor Gordon Dunstan argues that a distinction must be drawn between a conceptus that is destined for implantation and growth to maturity in the uterus, and one that is not so destined. In the first case the governing consideration must be the protection and promotion of the embryo's own intrinsic interest. In the second case the conceptus has no potential for long-term survival, and may ethically be used for research that will advance our understanding of human fertility and development, and hence enable future embryos to survive and to develop without handicap.

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Outcome of pregnancy following induced abortion

Report from the joint study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists

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Summary. A total of 1590 general practitioners and 795 gynaecologists in England, Scotland and Wales are participating in a long-term, prospective study concerning the sequelae of induced abortion. In the present report a comparison is made between the outcome of the first post-index pregnancy in 745 women whose index pregnancy ended in an induced abortion (cases) and that in 1339 women who had an unplanned index pregnancy but were not referred for induced abortion (controls). There were no statistically significant differences between cases and controls. The increased relative risk which was found amongst the induced abortion group of non-viable outcome, low birthweight and shortened gestation, could have arisen by chance. Further analysis of a larger number of pregnancies is required to permit confident interpretation of these observations. The present data provide no reason for alterations in the current management of induced abortion, or the subsequent pregnancy.

Among the many published reports about the sequelae of induced abortion, there are conflicting results, which could be due to differences in methods, the variable allowance for possible bias, and the differences in geographical, political and socioeconomic settings.

Changes have occurred so quickly in public and professional attitudes and practices that many issues once thought to be important no longer seem so, whilst the widespread use of abortion has revealed problems and posed new questions which were not, and could not have been, answered at an earlier date.

In a comprehensive review of the literature Hogue *et al.* (1982) considered two types of study design to be the most suitable for examining the problems, namely the pregnancy cohort and the abortion cohort designs.

The pregnancy cohort is a retrospective study where cases and controls are drawn from a group of currently pregnant women whose prior abortion status is determined from interview and records. This has the advantage of being economic and speedy, but cannot be used in the investigation of subfertility. The other disadvantage is the unreliability of patients' recall. In one study from Yugoslavia (Hogue 1975), 63% of women who had an induced abortion at their first pregnancy denied the abortion at subsequent interview and Madore *et al.* (1981) reported similar findings.

The abortion cohort study is prospective; the

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cases consist of women having an induced abortion whose subsequent medical progress is compared with a control group who did not have an induced abortion but were recruited at the same time. In this type of study the observations will be made as they occur and depend much less on unsatisfactory recall or reporting of previous history. The main disadvantage, however, is expense. All recruited women must be followed for several years and inevitably some will not have a further pregnancy and some will be lost to follow-up and yield no useful information.

The present joint study is an abortion cohort design. The setting of general practice in Britain provides a unique opportunity for long-term follow-up of patients, because general practitioners' records contain a substantially complete account of the patients' use of all health services.

Objectives

The present long-term, prospective, controlled study aims to compare the subsequent health of a group of women (cases) presenting to their general practitioner and having an induced abortion, with that of another group presenting to the same doctors with an unplanned pregnancy but not referred for an induced abortion (controls). Attention is being given to the course and outcome of pregnancy following induced abortion, to subsequent fertility and fecundity, and to all reported morbidity, both short- and long-term, but particularly monitoring psychiatric illnesses. In the present paper the outcome of the first post-index pregnancy is compared between cases and controls. The conditions examined are spontaneous fetal loss, shortened gestation and low birthweight.

Patients and methods

Details of methods, the characteristics of the recruited patients and the early reported sequelae of the induced abortion operations have been described elsewhere (Kay & Frank 1981; Frank *et al.* 1985). This study is jointly supported by the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists and has involved 1590 general practitioners and 795 gynaecologists. In summary, two main groups of women were recruited by general practitioners from England, Scotland and Wales, during a 2½-year period between 1976 and 1979 First, 7232 women referred by the study general practitioners for an induced abortion and, second, a control group of 7246 subjects presenting to the same doctors during the recruitment period with an unplanned pregnancy. Because originally only women with even dates of birth were recruited as controls, this yielded too few controls and, thus, for the second part of recruitment all such women were recruited regardless of their date of birth.

The design of the study did not permit the inclusion of patients who sought termination of pregnancy from private agencies without consulting their general practitioners.

For those pregnancies referred for induced abortion, the gynaecologist was asked to complete details of the consultation and (if performed) the operation and early complications. In the control group, details of index pregnancies and their outcome were obtained from the general practitioners 9 months after recruitment.

For all recruited patients a follow-up form has been sent for completion by the general practitioners every 6 months from the time of recruitment, so long as they have remained under observation. Information on this has included details of all newly presenting episodes of illness and newly occurring pregnancies.

Each patient was asked to estimate the length of time for which she had tried to conceive prior to her last menstrual period. Where women could give such an estimate the pregnancy was defined as planned, for those who could not, as unplanned. The index pregnancy was that current at the time of recruitment. Miscarriage is used throughout this paper to denote a spontaneous abortion or missed abortion, in order to avoid confusion with induced abortion. Non-viable outcome is the term used to denote miscarriage, ectopic pregnancy or stillbirth.

Inclusion and exclusion criteria

Of the women originally referred for induced abortion, it is those who were referred for a non-medical reason and who actually had the operation whose subsequent risks are of greatest interest Therefore we have excluded the others. In patients who had an induced abortion the median time between recruitment and the operation was 2 weeks and in order to make the control group's entry criteria comparable, controls were excluded from the analysis if their pregnancy terminated within 2 weeks of recruitment Excluding these early miscarriages from cases and controls avoids another possible bias which would arise if there was a tendency for women threatening miscarriage to be recruited as controls rather than cases (or vice versa) Gestation at entry to the analysis was, therefore, gestation at operation in the cases and gestation at recruitment plus 2 weeks in the controls. Entry into the analysis carried the implication that miscarriage had not occurred by this time.

Gestation at entry tended to be longer for controls than for cases, and so this group may have had an intrinsically lower risk of miscarriage than the cases. To compensate for this, the results have been adjusted for gestation at entry into the study, and control subjects entered beyond 22 weeks gestation have been excluded as there were no such pregnancies amongst the cases.

In the control population a post-index pregnancy had been conceived by a higher proportion of women who had lost their index pregnancy than in those whose index pregnancy ended in live birth (46% compared with 23%) Thus, women with an adverse outcome to the index pregnancy who might have constituted a poor-risk subgroup were over-represented amongst the control post-index pregnancies In order to assess the size of this potential bias the post-index pregnancies in controls were subdivided into those with a normal outcome or induced abortion, and those with a non-viable outcome to their index pregnancy, and the non-viable post-index pregnancy outcome rates were calculated separately for each group and for the two groups combined (Table 1). Although the adverse outcome rate was, as expected, higher in patients with a non-viable outcome to their index pregnancy, these women constituted only a small proportion of controls and the overall comparison of cases versus controls is little affected by whether or not these patients are included in the control comparison group For the present analysis, therefore, the combined groups have been used throughout.

Competing risks of miscarriage and induced abortion

The induced abortion rate in the first post-index pregnancies of cases was 28% compared with only 11% in the control group, and this has an effect on the observed rate of other types of outcome. By the time she has had an induced abortion a woman has already passed a substantial proportion of the risk of miscarriage or ectopic pregnancy. Complete inclusion or exclusion from the analysis of women who have had an induced abortion in the first post-index pregnancy would have the effect, therefore, of spuriously altering the relative miscarriage rate (Chung 1981; Schoenbaum *et al.* 1981). In comparing non-viable outcome rates in the first and second trimesters a life-table technique, by the logrank method (Peto *et al.* 1977), has, therefore, been used in this analysis.

Table 1. Outcome of post-index pregnancy in cases and controls[a]

Comparison group	Number of women with post-index pregnancy (N)	Observed number with non-viable outcome (O)	Expected number with non-viable outcome (E)	O/E
Cases	745	73	65 94	1·11
Controls				
Group A (non-viable outcome to index pregnancy)	145	19	15·69	1·21
Group B (viable outcome to index pregnancy)	1194	101	111·37	0·91
Groups A + B	1339	120	127·06	0·94

[a] Adjusted for age, marital status and gestation at entry into the study.

Reporting delay

If the analysis were to include all patients with post-index pregnancies as soon as these had been completed, there would be a bias towards those post-index pregnancies of shorter duration, that is those with adverse outcome. Therefore, post-index pregnancies have been included only when the last menstrual period was at least 18 months prior to the closure of this data file on 12 February 1983, which gives ample time for delayed reports on all completed pregnancies to be included.

Effect of differences between patient characteristics

Differences in patient characteristics between cases and controls could influence the outcome of post-index pregnancies. Since outcome is related to maternal age, the nine women under the age of 16, all in the 'case' group, were excluded.

To determine which characteristics influenced the outcome of the post-index pregnancies the features recorded at recruitment were first examined (Table 2). It can be seen that cases and controls were not importantly different. Second, comparison was made of the relationship between non-viable outcome, shortened gestation and low birthweight on the one hand and the characteristics listed in Table 2 on the other. From these two analyses, the difference between cases and controls was assessed for each characteristic, and also the magnitude of effect which such differences had on the risk of adverse outcome.

It was concluded that in addition to gestation at entry, age and marital status were the characteristics which most influenced the outcome of the post-index pregnancy. Adjustment for these factors has been made by stratification of the logrank analyses. The following strata have been used: gestation at entry (weeks) <10, 10–11, 12–13, 14–22; age (years) 16–17, 18–19, 20–24, 25–29, 30–34 and ≥35; marital status—married, single, or other.

Loss to follow-up

Loss to follow-up occurred almost exclusively when patients moved from their doctor's list, usually when moving from his area, or when the doctor withdrew from the study or died. In the present analysis, subjects lost to follow-up consisted of 2856 (39·5%) cases and 2825 (39%) controls. Their characteristics have been analysed and compared with the total population. Patients no longer under observation were slightly younger, had a lower parity, slightly higher social class, and contained more single women than the original study population. These findings apply equally to cases and controls, except for age where a significantly larger proportion of controls (50·3%) than of cases (45·8%) under the age of 20 were lost to follow-up. The overall losses modified, therefore, to only a minor extent most of the characteristics of the original study population. The effects of the age differences have been controlled by stratification. Therefore, there appears to be no reason why loss to follow-up should have introduced bias into the present analysis.

Table 2. Characteristics at recruitment of cases and controls

Characteristic	Cases	Controls
Age (years)	24·0	25·1
Number of cigarettes per day	7·5	6·6
% who smoke	49·0	44·0
Height (cm)	162·2	161·5
% not married	73·0	40·0
Gestation at entry (weeks)	10·7	12·9
Age when last in full-time education (years)	16·0	16·3
Interval between index and post-index pregnancy (months)	18·7	15·2
Number of previous live births	0·86	0·68
% with no previous pregnancy	50·0	56·0
% with previous miscarriage	9·5	9·6
% with previous stillbirth	0·5	0·8
% with previous induced abortion	10·9	9·2

Results are mean values (except where % stated)

Summary of inclusion data

Cases were women of 16 years and over at recruitment referred for and undergoing induced abortion in the index pregnancy, excluding those referred for medical and obstetric indications or because of the risk of congenital abnormalities in the baby. Controls were women initially recruited by 20 weeks of gestation, planning to go to term and whose index pregnancy did not terminate within 2 weeks of recruitment. In both cases and controls post-index pregnancies were limited to women having a last menstrual period before 12 August 1981. The effect of the application of these criteria is summarized in Table 3.

Presentation of data

In presenting the results for each group, the total number of women with a post-index pregnancy (N), the number with a non-viable outcome actually observed (O) and the number expected (E) if the non-viable outcome rates (within each stratum) had been as in the two groups combined, are given. The ratio O/E is a measure by which the result in one group is compared with that in the total population analysed. If the ratio is greater than unity then the group fared worse than average. Relative risks were calculated as $\text{Exp}\left(\frac{O_1-E_1}{V}\right)$ and their 95% confidence limits as $\text{Exp}\left(\frac{O_1-E_1}{V} \pm \frac{1{\cdot}96}{\sqrt{V}}\right)$ where O_1-E_1 denotes the difference between the observed and the expected number of events in the cases and V is the variance of this difference.

Excess risk was estimated by applying the adjusted relative risk to stated risks.

Results

Details of the operation in the cases are given in Table 4. Seventy four per cent of procedures were in NHS premises. This proportion is considerably higher than figures published for England and Wales by the OPCS (1979). The discrepancy arises because patients going direct to the private sector without consulting their general practitioner were not included. A great majority of operations were by vacuum aspiration (82%), dilatation with forceps evacuation accounting for 6%, and instillation procedures 11% of the total. One-half of the operations were performed between 10 and 13 weeks gestation, and 15% were ≥14 weeks.

Outcome of first post-index pregnancy

Looking at all post-index pregnancies regardless of obstetric history, there was an excess of a non-viable outcome in cases compared with controls, but this was not statistically significant (relative risk 1·24 with 95% confidence limits 0·88 to 1·75) (Table 5) The relative risk of a non-viable outcome comparing cases with controls was greatest in the third trimester of pregnancy, but the number of subjects was too small to draw conclusions These and other differences, including low birthweight and shortened gestation, were not statistically significant.

In the second analysis only those women whose index pregnancy was their first have been included. Thus, women in their second pregnancy who have had one previous induced abortion (cases) were compared with women in their second pregnancy who had a natural outcome to their first pregnancy (Table 6). It will be recalled that both groups have been matched as far as possible for their intrinsic risk of miscarriage, and so these groups, as they stand, are appropriate comparison groups regardless of the outcome of index pregnancy. Although the relative risk in these cases (1·61) of any non-viable outcome was greater than in the previous comparisons, it is still not statistically significant, and

Table 3. Exclusion of patients from the analysis

Reason for exclusion	Cases (*n*)	Controls (*n*)
Total no. with post-index pregnancy conceived before 1 August 1981	976	1574
Did not undergo induced abortion	143	—
Had induced abortion for medical reason or risk of congenital abnormality	79	—
Age <16 years	9	—
Miscarried within 2 weeks of recruitment	—	79
Gestation >20 weeks at recruitment	—	156
Total no. of exclusions	231	235
No. left for analysis	745	1339

sub-division of the outcome according to gestation at conclusion again showed no significant differences, nor was there a significant increase in low birthweight or shortened gestation in the cases.

Table 4. Details of the induced abortion in the index pregnancy in 745 patients (cases)

Place of abortion	
NHS premises	74%
Private premises	26%
Patient status	
In-patient	85%
Out-patient	15%
Gestation (weeks)	
<10	35%
10–13	50%
>13	15%
Method of operation	
Suction evacuation	82%
Dilatation and curettage with forceps evacuation	6%
Uterine instillation procedures	11%
Hysterotomy	0·4%
Other	1·0%
Dilator size (mm)	
Not used	19%
<9	20%
9–12	52%
13–21	7%
Not known	2%

Figs 1 and 2 show the life-table estimates of the percentages of pregnancies remaining viable as gestation progresses in the absence of induced abortion. For example, at week 40 (Fig. 1) the pregnancy survival rate was 88% for cases and 90% for controls. Thus, over the entire first post-index pregnancy, if no induced abortions had been performed, 12% of case pregnancies and 10% of control pregnancies would have ended in a non-viable outcome. These unadjusted results are consistent with the slight excess of adverse outcome in women whose index pregnancy ended in induced abortion and which was shown in the adjusted results described previously. The life tables also demonstrate that there was no striking variation in the differences between cases and controls at different stages of gestation.

Discussion

The interpretation of the sequelae of induced abortion is made complex by the multiplicity and variety of confounding factors which might affect them. These must be carefully considered when selecting the setting for such work, the patients to be observed, both cases and controls, and the method of analysis to be employed. Several authors (Obel 1979; Hogue *et al.* 1982) have indicated that these problems may not have been sufficiently considered in some previous studies. In the assessment of the present data

Table 5. Outcome of post-index pregnancy for cases and controls* (all women regardless of parity at recruitment)

Outcome of post-index pregnancy	Controls				Cases				Relative risk cases: controls (+95% confidence limits)	χ^2
	N	O	E	O/E	N	O	E	O/E		
Non-viable outcome										
1–13 weeks	1339	77	81·53	0·94	745	47	42·47	1·11	1·24 (0·81–1·90)	0·96 NS
14–28 weeks	1134	37	36·71	1·01	513	19	19·29	0·99	0·97 (0·51–1·83)	0·01 NS
≥29 weeks (stillbirths)	1075	6	8·81	0·67	470	7	4·19	1·67	3·38 (0·93–12·28)	3·42 NS
All gestations	1339	120	127·06	0·94	745	73	65·94	1·11	1·24 (0·88–1·75)	1·50 NS
Low birthweight (<2500 g)	1054	51	55·49	0·92	458	34	29·51	1·15	1·39 (0·82–2·36)	1·47 NS
Short gestation (≤37 weeks for livebirths)	1075	131	134·63	0·97	470	70	66·37	1·05	1·13 (0·79–1·62)	0·45 NS

*Results adjusted for age, marital status and gestation at entry to the study

N=Total no. with a post-index pregnancy available for analysis; O=observed no. of outcomes; E=expected no of outcomes (see text).

NS, Not statistically significant.

Table 6. Outcome of post-index pregnancy for cases and controls[a] (only women who were primigravid at recruitment)

Outcome of post-index pregnancy	Controls				Cases				Relative risk cases: controls	
	N	O	E	O/E	N	O	E	O/E	(+95% confidence limits)	χ^2
Non-viable outcome										
1–13 weeks	746	34	37·68	0·90	372	19	15·32	1·24	1·61 (0·80–3·26)	1·75 NS
14–28 weeks	670	21	22·92	0·92	273	12	10·08	1·19	1·46 (0·61–3·46)	0·72 NS
≥29 weeks (stillbirths)	637	4	5·04	0·79	250	3	1·96	1·53	2·49 (0·40–15·62)	0·95 NS
All gestations	746	59	65·63	0·90	372	34	27·37	1·24	1·61 (0·95–2·71)	3·15 NS
Low birthweight (<2500 g)	627	27	28·00	0·96	246	17	16·00	1·06	1·14 (0·56–2·34)	0·13 NS
Short gestation (≤37 weeks for livebirths)	637	66	69·03	0·96	250	38	34·97	1·09	1·22 (0·74–2·01)	0·60 NS

[a] Results adjusted for age, marital status and gestation at entry to the study.

N=Total no. with a post-index pregnancy available for analysis; O=observed no. of outcomes, E=expected no. of outcomes (see text).

NS, Not statistically significant

adjustments have been made for a number of potentially confounding variables. These have included separate consideration of non-viable outcomes by trimester of post-index pregnancies, the use of life-table analysis to overcome the problems of induced abortion competing with miscarriage as a possible outcome in the post-index pregnancies and stratification for relevant patient characteristics, and for gestation at entry into the study. Consideration has also been given to the effect of loss to follow-up. The possibility of biased recruitment of cases and controls according to susceptibility to adverse outcome has been minimized by the exclusion criteria adopted.

The under-reporting of early miscarriage mentioned by several authors (Schoenbaum *et al.* 1981; Chung *et al.* 1982) cannot be eliminated, but it should be reduced in the present study because recruited patients have been observed prospectively in the setting of primary care. Early miscarriages are more likely to be reported to the family doctor than to other health service agencies. In the post-index preg-

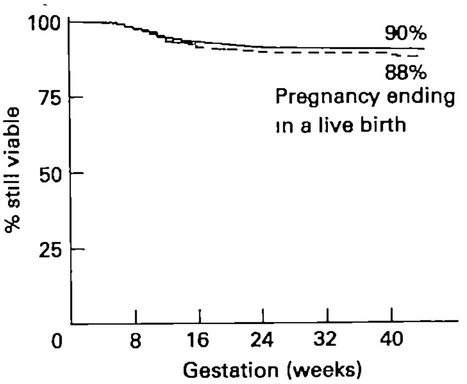

Fig. 1. Life-table analysis of viability according to gestation in the post-index pregnancy for all patients (—-—) cases; (——) controls.

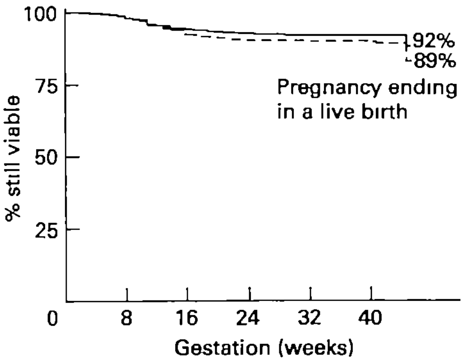

Fig. 2. Life-table analysis of viability according to gestation in the post-index pregnancy for patients who were primigravid at recruitment (—-—) cases; (——) controls

nancy under-reporting is likely to apply equally to cases and controls.

The results of the present analysis support other recent studies which have found only small or no increased adverse outcome in pregnancies following induced abortion. Thus, Harlap *et al.* (1979), using a life-table method to analyse the relationship between miscarriage and previous induced abortion in California, observed that the only significant risk was confined to women who had had their operation before 1973 when abortion was mostly illegal and carried out by dilatation and curettage. A retrospective study from the USA (Kline *et al.*, 1978) also failed to find a connection between miscarriage and previous induced abortion. A major abortion cohort study reported by Chung *et al.* (1982) from Hawaii found a relative risk of pregnancy loss following induced abortion of 1·10, 0·88 and 0·81 for the first to third trimester, respectively, and in a carefully controlled and analysed pregnancy cohort study Schoenbaum *et al.* (1980) concluded that women able to reach 27 weeks gestation after a previous induced abortion are not at special risk of stillbirth or low birthweight. Studies from Holland (van der Slikke & Treffers 1978) and Norway (Obel 1980) also failed to find an adverse association.

Some adverse effects have, however, been reported. In a pregnancy cohort analysis Madore *et al.* (1981) found a statistically significant increase of non-viable outcome in pregnancies following induced abortion. Other studies (WHO Task Force on Sequelae of Abortion 1979; Berkowitz 1981; Meirik & Bergstrom 1982) reported a significant association between prematurity and a previous abortion by vacuum aspiration. One of these studies was sponsored by the World Health Organization Task Force on Sequelae of Abortion (1979) and involved data from city clusters in East and West Europe. The increased risk was only found in one city cluster.

In a comprehensive review by Hogue *et al.* (1982) only three out of nine studies showed a statistically significant increase in second trimester abortion in the pregnancy following induced abortion. In two of these, dilatation and curettage had been used for the operation and the third found an increased risk in only one racial group. The same authors described an increased relative risk of shortened gestation (but not low birthweight) which reached statistical significance in only two out of 12 studies, one of which consisted of patients having saline infusion procedures and the other was the study reported by the WHO Task Force on Sequelae of Abortion (1979). Out of 17 studies where low birthweight in the pregnancy following induced abortion was examined, the relative risk was significantly increased in only five. In three of these dilatation and curettage had been used for the operation.

Several questions must be asked when interpreting the sequelae of induced abortion. Do they form a basis for changes in abortion procedures? Are they sufficient to alter the practical management of subsequent pregnancies? The results of the present study indicate a consistent increase in the relative risk of adverse outcome in the pregnancy following induced abortion, but these differences could have arisen by chance. This applied whether examining all women, regardless of previous pregnancy history, or only those women whose index pregnancy was their first. Sub-division by fetal loss according to trimester, shortened gestation and low birthweight all gave statistically non-significant increased relative risks in the post-abortion pregnancies compared with the control group.

Combination of all three trimesters gave an increased relative risk of 1·24 of adverse outcome following induced abortion (regardless of previous pregnancy history). The excess risk implied by this relative risk depends on the underlying natural risk in the absence of induced abortion. If the risk following induced abortion is 12 per 100 pregnancies (as in the life-table estimate for cases (Fig. 1)) then a relative risk of 1·24 implies that $12 \times 0{\cdot}24/1{\cdot}24 = 2$ per 100 of the 12 are the excess. A relative risk of 1·61 was obtained when only women in their first pregnancy at recruitment were analysed and by similar calculations as in Fig. 2, this represents an excess risk of 4 per 100 pregnancies. Even if these findings were confirmed as real, it seems unlikely that their magnitude would be great enough to alter the patient's or the doctor's attitude to abortion, or its management, nor would they change the management of subsequent pregnancy. The number of first post-index pregnancies in the present study is not yet sufficient to make a detailed analysis of the influence of factors such as gestation at induced abortion, the method of termination, dilator size or the premises where the operation was performed. If some of these were to show an important association with adverse outcome, modifications might be desirable, but as a result of other studies

(Grimes & Cates 1979) there is now a wider acceptance of the use of vacuum aspiration as a preferred method for terminating early pregnancies. In the present analysis 85% of women had first trimester induced abortions and 82% of operations were carried out by vacuum aspiration technique. Thus, the number of patients who were terminated by other methods at a late gestation and who have had a post-index pregnancy is not yet sufficient for informative analysis.

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Improvements in the registration and analysis of fetal heart rate records at the bedside

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Summary. A microprocessor system is described for on-line analysis of the fetal heart rate detected by conventional Doppler systems. A brief account is given of the instrumentation and program structure. The system has been tested by analysing normal and abnormal antenatal fetal heart rate records. Pulse Doppler with autocorrelation measurement of the fetal pulse interval reduced the signal loss in clinical practice by a factor of 10, to an average of 2·1% in 629 records from uncomplicated pregnancies. Yet it is still necessary to identify signal loss, because it occasionally rises to unacceptable levels in association with fetal movements or hiccups. Medium-term measures of fetal heart rate variation (within 16–0·1 cycles/min) varied with gestational age, but were a better index of fetal well-being than longer-term measures. The application of the system to fetal monitoring is illustrated.

The accurate recording and interpretation of human fetal heart rate, when measured with Doppler ultrasound, has presented formidable problems. Signal loss has been high, especially before 32 weeks gestation, approaching 50% at times (Dawes *et al.* 1981), but can be reduced either with a range-gate to reduce noise (Lawson *et al.* 1982) or by autocorrelation (e.g. Lawson *et al.* 1983). The limits of autocorrelation have not been explored. In this study therefore, we have asked whether its performance is so good that signal loss can be ignored.

Secondly, visual interpretation of records has been criticized on the grounds of inter- and intra-observer variation (Trimbos & Keirse 1978, Lotgering *et al.* 1982). For this reason we have developed a system of numerical analysis using either minicomputers off-line or, more recently, a microprocessor system at the bedside.

A central question is what measure of heart rate variation gives the best indications of fetal well-being. To answer this question we need to know the frequency distribution of the various measures in the population, and a start has been made in this direction (e.g. Dawes *et al.* 1982*b*). We also need more information about the patterns developed in abnormal fetuses, as well as information on very-long-term measures of heart rate variation as compared with shorter-term measures. Beat-to-beat variation is distorted by Doppler ultrasound detection so that it cannot be used as a valid measure antenatally, even with the present generation of instruments.

The new results to be described show an improvement in the registration of records using Doppler ultrasound autocorrelation, and suggest that medium-term measures of heart rate variation are the most useful.

Patients and methods

Patient selection

The patients studied consisted of two groups. There were, first, patients selected as normal at the time when a fetal heart rate record was taken, each for 30 mins, at 28, 32, 36 or 40 weeks gestation.

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Secondly, sequential records were taken over a period of 8 months from a high-risk clinic. There was less pressure to minimize recording time than in the routine outpatient service (see Table 1).

The groups were subdivided according to whether the baby was normal at delivery: weight >25th centile for age and sex, no fetal distress in labour, no intubation or admission to the special care baby unit. The data on those who continued normally have been presented separately (see Table 2).

Instrumentation

A Doppler ultrasound heart rate monitor with autocorrelation (Hewlett Packard 8040A) is used to detect the fetal pulse and to give an indirect estimate of intrauterine pressure from an external tocodynamometer. Fetal movements are recorded by the patient pressing a button. The record is analysed intermittently at the bedside and the results displayed interactively to the nurse, so as to maintain record quality.

The system consists of a master microprocessor (Nascom II, with 64K memory and dual floppy disc drive), a slave based on a 6502 microprocessor (Mos Technology Inc; Wickham *et al.* 1983), keyboard and visual display unit. The slave receives the signal from the ultrasound monitor, examines fetal pulse intervals using an error algorithm (Dalton *et al.* 1977) and averages valid pulse intervals over 3·75 s (1/16 min). After each 1/16 min the data are combined into 2 bytes (10 bits for mean pulse interval, 5 bits for uterine pressure and 1 bit for fetal movement) and transferred to the master. Pulse interval is recorded to the nearest ms, uterine pressure to 1/32 of full scale (5V) and a fetal movement as absent or present.

The Hewlett-Packard monitor is interfaced with the slave microprocessor by a voltage/frequency convertor, adjusted to generate a brief fast rising voltage pulse at intervals corresponding to the calculated heart rate, interrupted when a valid input is not present. When the microprocessor is switched on, an instruction is given to press the calibration switch on the Hewlett-Packard monitor. This injects a 200-beats/min signal displayed on a visual display unit (VDU). If this signal differs from 200 beats/min by > 1% the interface must be adjusted: otherwise the program proceeds, but the differences of 0·25–1% are automatically corrected. The interface between the slave and master microprocessors has been described elsewhere (Wickham *et al.* 1983)

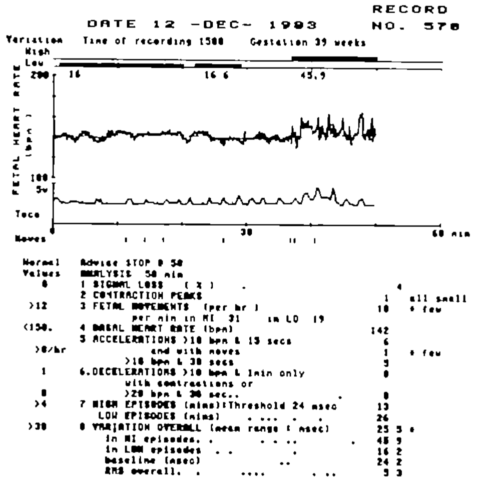
Numerical analysis

A baseline is fitted to the fetal heart rate trace (Dawes *et al.* 1982*a*). Heart rate variation is measured as the root mean square of the deviations from this baseline for each minute (RMS value, derived from pulse intervals in ms), and/or as the range in pulse interval each minute (ms). The range is calculated as the difference between minimum and maximum pulse interval unless, as during a prolonged acceleration, all pulse intervals are less than baseline when the range is measured from the baseline. The ***mean minute RMS*** value and the ***mean minute range*** are then measured over the total time elapsed.

Episodes of high or low variation are identified as 5 of 6 sequential minutes each with a minute range >32 or <30 ms respectively (4 of 5 min if at the start or end of a record); minutes during which a deceleration (⩾10 beats/min lasting > 1 min; or >20 beats/min lasting ⩾30 s) is present are excluded in the identification of episodes of high variation. These criteria have been derived empirically from normal records taken at 28–41 weeks gestation. We have recently shown that some growth-retarded fetuses express episodes of high and low heart rate variation normally but at a lower overall mean minute range (Henson *et al.* 1984). In these traces it becomes important to be able to recognize small decelerations superimposed on a flat baseline. Hence if after 25 min the plot is recognized as of very low variability (<25 ms mean range), then the analysis is modified. Constraints are placed on the construction of the baseline to enable shallow decelerations to be identified, and episodes of high and low variation are measured as >24 or <22 ms minute range respectively.

Patient information

The operator is guided by simple directions issued by the program. Each record is started by an instruction to enter the patient's surname and first name, her hospital number, the time and estimated gestational age in weeks. Because patient identity depends on hospital number (e.g. for reference to previous records on file), the operator is asked to check its accuracy care-



```
                                                   RECORD
           DATE 12 -DEC- 1983                      NO. 578
Variation  Time of recording 1500   Gestation 39 weeks

Normal   Advise STOP @ 50
Values   ANALYSIS  50 min
  0      1 SIGNAL LOSS   ( % )    .                      4
         2 CONTRACTION PEAKS                           1   all small
 >12     3 FETAL MOVEMENTS  (per hr )                 10   * few
                per min in HI  31    in LO  19
 <150.   4 BASAL HEART RATE (bpm)                    142
         5 ACCELERATIONS >10 bpm & 15 secs             6
  >0/hr            and with moves                      1   * few
                >10 bpm & 30 secs                      5
  1      6.DECELERATIONS >10 bpm & 1min only           0
                with contractions or
  0             >20 bpm & 30 sec..        .            0
  >4     7 HIGH EPISODES (mins):Threshold 24 msec     13
            LOW EPISODES (mins)    . ...  .   .       26
 >30     8 VARIATION OVERALL (mean range : msec)      25 5 *
              in HI episodes. .     . . ..      .     45 9
              in LOW episodes  . .       .            16 2
              baseline (msec)          ..             24 2
              RMS overall.  .     ....      . ..       5 3
```

Fig. 1. Example of a record taken at 39 weeks gestation with an unusually long episode of low heart rate variation initially The outcome was vaginal delivery of a normal infant In this and subsequent figures the numbers below the plot of high/low fetal heart rate variation shows the mean minute range in ms.

fully. The program then prints the heading (upper part of Fig 1) and the axes of the plot. Recording is started as soon as a good signal is obtained.

Interactive display

A plot of the fetal heart rate against time in minutes during the current 5 min is displayed. Current signal loss is shown as a percentage. The operator's attention is drawn to high signal loss (number of 1/16-min epochs for which there was no valid pulse interval, exceeding 10 in any 5 min *and* 30%) by flashing the message 'signal loss'. At the end of each 5 min the data are plotted on a printer (Adcomp X80SP) and the VDU display is restarted.

Data analysis is undertaken after 10 min, every 5 min thereafter until 30 min, and then every 10 min until 60 min. Recording is stopped after 60 min, but the nurse may interrupt the record at any time (see below). After each analysis the results are presented in the lower half of the display unit. If the overall signal loss is more than 40% the comment 'high' will appear, and if the recording time is also less than 15 min, the operator is advised to 'restart?'. If less than 12 moves/h have been detected, or if the record of uterine contractions is very flat the word 'check' flashes for 1 min by the appropriate heading. A continuing display advises the operator to 'continue' or 'stop'. At this early stage in the development of the system the criteria for issuing these instructions have been devised arbitrarily and have not been validated in clinical practice. They were based on evidence of episodic changes in heart rate variation corresponding to sleep states postnatally. In the absence of a large deceleration (>20 missed beats, a measure of area beneath the baseline) the advice to 'stop' is shown, flashing for 1 min, when an episode of high fetal heart rate variation has been identified.

Interrupts and printing

The program can be interrupted at any time except when an analysis is in progress, or when plotting or filing data, when the central processing unit is otherwise engaged. After interruption the heart rate recording may be stopped and the results of the last analysis printed, or the data may be discarded and a new record started, or the program may be continued without loss of data (because they continue to be accumulated by the slave microprocessor). If an attempt is made to end a record before the advice to 'stop' has been given, the operator is asked whether he is sure. The program records whether and when the advice to stop is first given (see Figs 1 and 7). Thus guidance is offered for the most economical use of time, but is not mandatory.

When the last analysis has been completed, after 60 min or on interruption, the baseline is plotted (e.g. Fig 1; interrupted line), episodes of high and low variation are plotted with their mean minute ranges in ms, and the results of the last analysis are printed (Fig 1). Normal values are printed to the left and comments to the right, preceded by an asterisk if of importance. If decelerations are recognized (e.g. >20 missed beats in an otherwise normal trace), information on the characteristics is printed (e.g. Fig 7).

Initiation and filing

At the start of each day the system checks the date and month and, through an internal calendar, identifies the day of the week. If this is Monday the system will not proceed until a back up copy of the files has been made to protect against data loss from systems failure. If any

Table 1. Distribution of signal loss with gestational age

Gestational age (weeks)	No. of records	Mean length (min)	Mean signal loss (SEM) (%)
26–27	22	40	4·6 (1·04)
28–29	60	39	3·9 (0·48)
30–31	34	25	2 5 (0·77)
32–33	198	20	2·1 (0·24)
34–35	108	25	2·5 (0 37)
36–37	110	27	2 5 (0·41)
38–39	67	43	1·7 (0·39)
40–41	30	41	1·3 (0·41)

current file is filled, instructions are given to copy and replace the disc as necessary.

Two sets of files were made for each record, a 'patient' file and 'data' file. The 'patient' file holds the record and hospital numbers, time, date, name, the results of the last analysis, the location of the 'data' file and identification of the instrument and analytical program (32 items). Each 'patient' file holds up to 300 records, and two are stored on each disc, so that summaries of the last 300 records are instantly available. At the end of each record the files are searched and records bearing the same hospital number are identified, the names checked and a summary printed, e.g. Table 3. The 'data' files hold up to 75 h of original data (16 × 2 bytes/min).

Various options are available for recalling stored data The system can provide a register either of all the patient files or of those entered since the beginning of the present week, a complete printout of any one patient file identified by record number, or of any data file. It can also make a reprint of a record selected by number, of which any fraction or the whole can be chosen for re-analysis. The 10 programs are written in Basic and, with machine code subroutines, occupy 53kb. Analysis of 60 min of data takes about 4·5 min.

Results

The Hewlett-Packard 8040A proved easy to use, with few adjustments necessary to maintain a good quality record even at 28 weeks gestation. The nurse could therefore run records from two patients at once if necessary.

The mean signal loss (Table 1) was low compared with that using Doppler ultrasound detection without range gate or autocorrelation. In a previous study the signal loss was 10 times higher (21%) with a Hewlett-Packard 8031A monitor and the same type of program on line at 32 weeks gestation (Lawson *et al.* 1984). There was a greater mean signal loss earlier in gestation (4·1% at 26–29 weeks compared with 2·2% at 30–33 weeks; $P<0{\cdot}001$). It is of importance that the range of variation in signal loss was wide at all ages. Of the 629 records in Table 1, 36 (5·7%) had a signal loss >10%, and two exceeded 20% (21·3%) at 28 weeks; 21·9% at 36 weeks). The proportion with signal loss greater than 10% was the same at 26–29 weeks (6/82, 7·3%) and 36–39 weeks (13/177, 7·3%). Excessive signal loss was associated either with vigorous fetal movements or with an episode of hiccups (Fig 2). The latter introduces a repeating feature into the autocorrelation which confuses identification of pulse intervals. When signal loss is excessive (e.g. from 40–50 min in Fig 2) heart rate variation may appear to be reduced.

Measures of heart rate variation

Table 2 shows the mean values of four measures of fetal heart rate variation at different gesta-

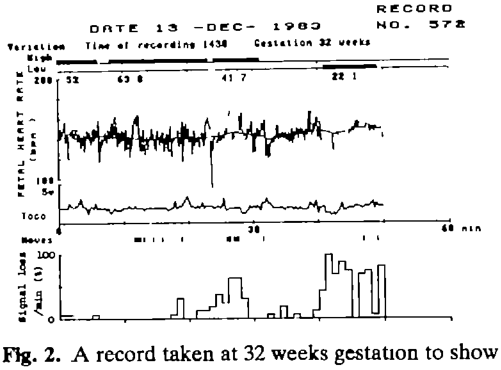


Fig. 2. A record taken at 32 weeks gestation to show excessive signal loss (lowest trace) associated with fetal movements at 26–28 min, or hiccups which were present between 41 and 50 min.

Table 2. Changes in four measures of fetal heart rate variations at different gestational ages from 30-min records, unselected or selected for normality at birth[a]

Gestational age (weeks)[b]		Numbers	Number of accelerations (>10 beats/min + 15 s)	Mean range of variation (ms)	High heart rate variation (min)	Mean baseline variation (ms)
28		60	4·5 (0·4)	39·5 (1·0)	12·9 (1·1)	30·0 (1·4)
	Selected	47	3·8 (0·4)	37·7 (1·1)	11·6 (1·2)	28·3 (1·5)
32		50	6·5 (0·5)	43·6 (1·5)	15·7 (1·2)	31·5 (1·4)
	Selected	32	6·7 (0·6)	44·4 (1·5)	17·1 (1·3)	30·4 (1·6)
36		60	7·0 (0·5)	45·6 (1·8)	14·0 (1·0)	31·6 (1·2)
	Selected	44	7·3 (0·6)	46·4 (2·1)	14·9 (1·2)	31·4 (1·5)
40		51	8·2 (0·6)	49·0 (2·2)	16·0 (1·2)	31·5 (1·7)
	Selected	37	8·4 (0·7)	48·9 (2·8)	16·2 (1·4)	32·6 (2·1)

[a] Birthweight >25th centile for age and sex; delivered at or after 37 weeks without antenatal distress or postnatal complications (see text).

[b] ±7 days.

Results are mean (SEM).

tional ages, unselected or selected for normality at birth. The results were similar in both groups.

The measures of medium-term variation are the number of accelerations (>10 beats/min and 15 s), the mean range of variation (defined in methods) and the number of minutes of high heart rate variation, i.e. spanning 5 min. The baseline variation is distinct, being a longer-term measure of variation (over 30 min in Table 2), from which high-frequency components have been filtered.

All the three measures in the first category increased with gestational age. The number of accelerations (per 30-min record) approximately doubled; the mean range of variation increased from 38 to 49 ms (by 30% in selected normals); and the duration rose (by 40% in the same group). The latter change occurred between 28 and 32 weeks.

We have used both the RMS and the mean range about the baseline to assess the medium-term variation (Dawes *et al.* 1981, 1982*b*; Visser *et al.* 1981; Henson *et al.* 1983, 1984; Lawson *et al.* 1984). The latter was preferred when signal loss was high, and is more rapidly calculated. The correlation between the two values was high ($r = 0{\cdot}97$) in 400 sequental records from a high-risk clinic, when using autocorrelation with low signal loss (Fig 3).

In contrast the long-term variations of baseline showed no significant change with gestational age. The mean value in 160 normal fetuses was 30·6 (SEM 0·84)ms. Fig 4 shows its distribution, with the lowest 5th centile <16 ms. There was no correlation between baseline variation and the mean range of variation, either in the records of Table 2 or in 400 unselected sequential records. As was to be expected baseline vari-

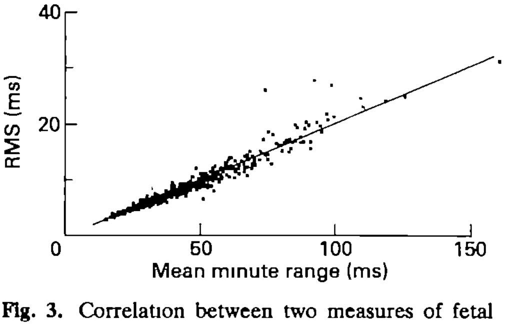


Fig. 3. Correlation between two measures of fetal heart rate variation, the root mean square (RMS) deviation from the mean value of fetal pulse interval and the mean minute range (ms), in 400 sequential records ($r = 0{\cdot}97$).

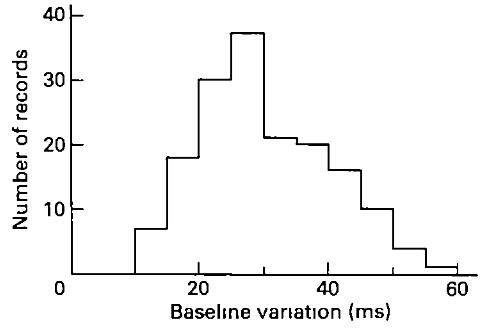


Fig. 4. Frequency distribution of baseline variation in 160 records, each 30 min long, from fetuses with a normal outcome at delivery (selected data of Table 2)

ation varied significantly with record length from a mean value of 28·2 (SEM 0·91) ms over 20 min (n = 135) to 32·6 (SEM 1·21) over 60 min (n = 92; P<0·001). What is of more practical importance is that baseline variation can be low (<20 ms) in fetuses with normal long-term variation and a normal outcome at birth. It can be very low in a flat fetal heart rate record with poor outcome (10 ms as in Fig 5*b*). In an equally sinister record (Fig 7) it was of normal value (34·9 ms) though the mean minute range was only 14·5 ms. From experience so far it does not appear to be a useful measure clinically.

We also have considered the possibility that the measure of fetal heart rate variation might be improved by calculating sequential pulse intervals over time intervals smaller or larger than 1 min *Beat-to-beat* variation cannot be measured using ultrasound detector systems which distort the signal. It is underestimated if ultrasound autocorrelation is used (Lawson *et al.* 1983), and overestimated by conventional Doppler detector systems (Lawson *et al.* 1982). And in the gestational age range 28–34 weeks we cannot use ECG fetal heart rate detection without excessive signal loss. We compared sections from typical records showing extreme characteristics, as in Fig 5. A record (14 September) from a normal pregnancy at 39 weeks gestation includes an episode of low heart rate variation (mean range 19·3 ms). This was compared with a section of record from a flat trace, between two pairs of decelerations, in a fetus which died *in utero* 2 days later at 26 weeks (mean range 4·8 ms; Fig 5, 17 October) Heart rate variation was calculated over 8 min, as the mean RMS value over 2, 4, 8, 16, 32, 64 and 128 epochs of 1/16 min. Fig 6 shows the results. Variation rose with increasing sample size, as in normal records from fetal lambs (Dalton *et al.* 1977) and man (Wheeler *et al.* 1979; Dawes *et al.* 1981). So there were low-frequency components present in both records. Because of the operation of the digital filter (with 50% attenuation at 0·1 min^{-1}) the RMS values tend towards a plateau with increasing sample size. In this instance the difference between the records was a little greater when expressed as the ratio of RMS values, at two epochs (4·8) than at 16 epochs (1 min; 3·8). But the difference was small and there are logistical reasons for preferring 1-min samples. The mean minute range was four times higher in the normal than in the abnormal record.

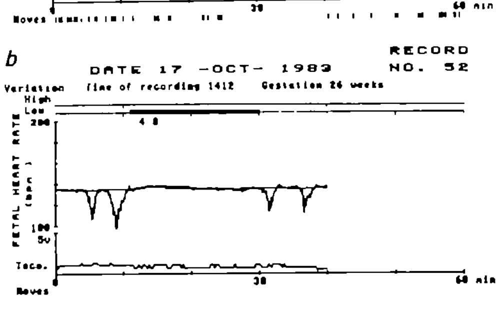


Fig. 5. Examples of records with relatively flat episodes, (*a*) (no 368) from a fetus at 39 weeks with normal outcome during a brief absence of movements, and (*b*) (no 52) from a fetus at 26 weeks which died 2 days later *in utero*, and which already had sinister brief decelerations.

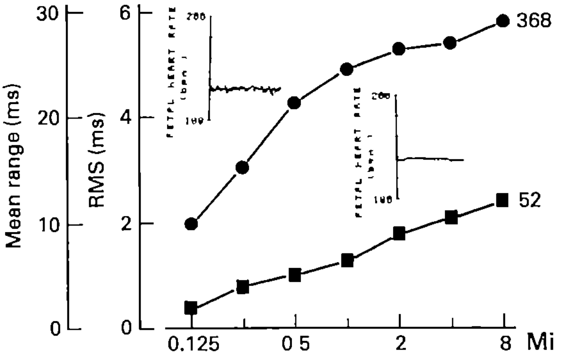


Fig. 6. More detailed analysis of short sections from the two records of Fig 5, identified by number 368 (above) and 52 (below) to show that both contained low-frequency components of heart rate variation, hardly perceptible in the original traces

The analytical system in practical use

Finally we illustrate the clinical application of the analysis. A patient with mild pre-eclampsia but no proteinuria had a relatively flat trace (mean range 26·4 ms, <5th centile) at 31 weeks gestation (Table 3). Signal loss was low. By 33–34 weeks the record was within the normal range (39–40 ms), but fetal growth was impaired and she was admitted for observation. A short

Table 3. Changes in the fetal heart rate record of a fetus with intrauterine growth retardation, delivered by caesarean section on 20 December on evidence of deterioration (see Fig 7)

Date	Gestational age (weeks)	Record length (min)	Signal loss (%)	Basal heart rate (beats/min)	High heart rate variation (min)[a]	Mean range of variation (ms)	Fetal movements (per h)
15 Nov	31	40	3·1	145	6 (29·5)	26·4	31
23 Nov	32	30	3·8	149	7 (26·9)	23·2	26
2 Dec	33	20	0	151	9 (44·3)	39 2	60
9 Dec	34	20	5·0	149	15 (44·5)	42·2	129
16 Dec	35	20	0	136	5 (50·3)	27·7	15
20 Dec	35	60	0·9	146	0	14·5*	22

[a] Max value in brackets.

* One large deceleration (97 lost beats over 2 5 min) associated with a small contraction was recognized. At delivery the cord was around the neck.

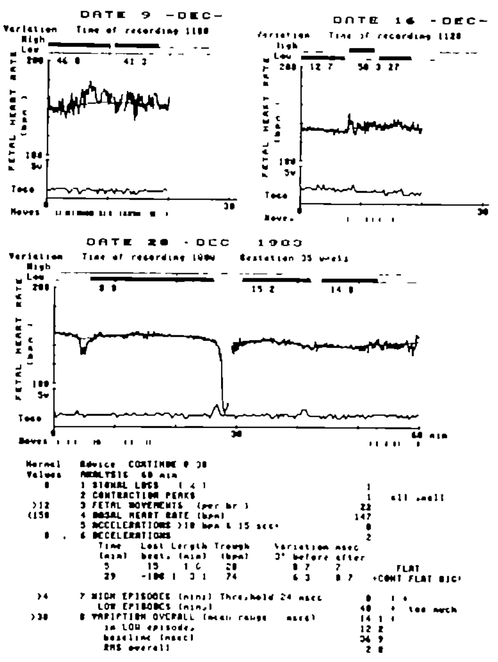


Fig. 7. Records selected from a larger series (summarized in Table 3) to show progressive changes in the fetal heart rate and movement patterns in a high risk pregnancy. At delivery 3 h after the last trace a growth-retarded (1·8 kg) infant was born with the cord round the neck but no evidence of acidaemia

record in week 35 showed a decrease in the mean minute range heart rate variation to 27·7 ms, with one episode of unusually low variation (12·7 ms) and fewer movements. Four days later the trace had become very flat (14·5 ms overall) with a large deceleration associated with a uterine contraction (Fig 7). At caesarean section later that day a small-for-dates (1·8 kg) infant was born with no gross evidence of acidaemia (umbilical artery blood pH 7·28 and base excess −6; Apgar scores 7 and 10 at 1 and 5 min respectively), but with the cord round the neck. It was notable that antenatally there was no consistent change in mean heart rate nor in the fetal movement count.

Discussion

We set out to determine whether autocorrelation (Hewlett-Packard 8040A) improved record quality sufficiently to dispense with the measurement of signal loss. It is evident that signal loss can still cause brief but gross distortions (Fig 2). It must continue to be measured and the analytical system will be improved if episodes of high loss are identified.

Our second objective has been to compare medium- and longer-range measures of fetal heart rate variation. Short-term (beat-to-beat) variation is modulated by fetal breathing movements, and is only a small proportion of fetal heart rate variation, even over as short a period as 5 min. It cannot be measured accurately by pulsed Doppler ultrasound (Lawson *et al.* 1983). The next longer (lower frequency) component that might usefully be considered is the variation between successive 1/16-min epochs. We have examined this component but found that, with present methods, it cannot be used to detect fetal breathing with certainty. We have not considered it in more detail.

The medium-term fetal heart rate variation (between 16 and 0·1 cycles/min) has been measured either as the standard deviation or the RMS (root mean square deviations from the mean) value over 1–2 min, or as the mean minute range of pulse interval around the baseline. The results correlate well (Fig 3). These medium-term (hitherto usually described as long-term) measures of heart rate variation comprise the brief accelerations associated with fetal movements, provided these do not fuse to cause a prolonged elevation of basal heart rate as in the upper part of Fig 5 (record no 368 at 5–10 min). Recent observations on fetal lambs have shown that muscular paralysis with gallamine does not abolish episodic brief cardiac accelerations (Clewlow & Dawes 1983; Bocking *et al.* 1983). The accelerations are, therefore, not the consequence of fetal movements but of central nervous, probably lower brainstem, activity, which coincide with spontaneous limb or trunk movements. They are absent from lambs which have lost the brain above the cervical cord, but not from those with transection of the upper brainstem above the pons (Dawes *et al.* 1983). It is evident that this component of the fetal heart contains an indication of health. It effectively identifies what is described visually as a flat trace and, as Figs 5 and 6 show it provides a quantitative measure which is a substantial improvement on visual inspection. It is still uncertain, however, whether it will provide a more critical separation of pathologically abnormal traces from the lowest few centiles of the population of normal records.

The very-long-term (baseline >30 min) measure of fetal heart rate variation was large (averaging 30 ms) and had a wide scatter in human fetuses with a normal outcome (Fig 3). So far as we can now judge its measurement did not improve discernment of abnormality. For example the baseline variation in the lowest record of Fig 7 (20 December) was above average, 36·9 ms. The separation by digital filtering reduced the background noise against which more definitive measures (of medium-term variation) are identified. In other words sick fetuses appear to lose most of the medium-term but less of the very-long-term components of heart rate variation. Is this simply the consequence of loss of that variation normally associated with fetal movements? And if so by what means is it effected? There is some speculation among physiologists that it could be either a consequence of natural opiate release, acting perhaps on medullary or lower brainstem centres, or through a generalized depression of those regions through oxygen lack. If so, it seems to occur without persistent metabolic acidaemia (Henson *et al.* 1983). There is no definite evidence on which to come to a conclusion. But the first step has been taken, to identify the question.

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Correlation of the interpretation of fetal heart rate records with cord plasma erythropoietin levels

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Summary. On the basis that fetal levels of plasma erythropoietin (Ep) may reflect fetal oxygenation the primary purpose of the present study was to assess the relation between Ep measured in cord plasma at delivery and the intrapartum fetal heart rate (FHR) record. A scoring system for interpreting FHR recordings blindly was prospectively utilized in 41 selected human pregnancies during the 4 h immediately preceding birth. The correlation of the overall mean FHR score for each individual patient with cord plasma Ep was significant such that the highest Ep levels were observed in those infants with the most abnormal FHR scores. Furthermore, when the birthweights of the infants were adjusted for gestational age, sex, and birth order, birthweight centile was negatively correlated with cord plasma Ep. When both FHR score and birthweight were simultaneously correlated with cord plasma Ep using multiple regression, the combined effect of these two factors improved the association of either alone with both contributing approximately equally.

Electronic fetal heart rate (FHR) monitoring has become a routine clinical technique for assessing the intrapartum condition of the fetus (Hobbins *et al.* 1979). Although the sensitivity of this technique in identifying fetuses at risk of hypoxic injury is clinically acceptable, its specificity is low. Ancillary clinical indicators for identifying fetuses at risk of hypoxic injury must be sought to increase the specificity of interpreting FHR records.

Erythropoietin (Ep), a glycoprotein hormone, is produced after several hours of hypoxaemia in both adult and fetal animals (Zanjani & Gordon 1971; Erslev 1975; Widness *et al.* 1983). During pregnancy this hormone does not cross the placenta in either direction (Jacobson *et al.* 1959; Zanjani & Gordon 1971). Data from human pregnancies indicate that by 32 weeks gestation the fetus is capable of responding to chronic hypoxaemia *in utero* by increasing Ep production (Finne 1968). Recently we have documented that a group of fetuses born after a normal labour and delivery had a significantly higher mean umbilical plasma immunoreactive Ep level than did a group of gestationally age-matched controls born after elective caesarean section without labour (Widness *et al.* 1984). We speculated that the group of fetuses undergoing labour may have been subjected to more pronounced prepartum fetal hypoxaemia which was reflected by increased plasma Ep levels. The

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purpose of the current prospective investigation was to determine if fetal plasma Ep measured at birth is associated with fetal intrapartum hypoxaemic events as indicated by electronic FHR monitoring.

Subjects and methods

Study pregnancies included those in whom gestational age was 32 weeks and who had intrapartum fetal cardiotocographic monitoring using an external Doppler and/or internal scalp electrode. Gestational age was estimated from the first day of the last menstrual period, as described by Thomson *et al.* (1968) (n=38); or when this information was unavailable, from fetal sonographic measurements taken between 15 to 24 weeks gestation (n=3). These studies were approved by the Research and Human Subjects Committee at Women and Infants Hospital. Written consent was obtained from all subjects.

The choice of pregnancies for study was selective. To examine the temporal relation of Ep with the interpretation of the FHR record, pregnancies having the longest FHR records were selected. Two groups of pregnancies were sought: those in whom the patient's primary physician interpreted the entire FHR record as indicative of fetal distress (n=34), or as not indicative of fetal distress (n=7). The primary physician's judgment regarding the FHR record was not utilized in any portion of the data analysis. This selection procedure was intended as a means to increase the likelihood of having FHR abnormalities identified by the two experienced perinatologists (K.A.T. and D.R.C.) whose judgments of the FHR records were used in the data analyses.

The *post hoc* interpretation of the FHR records was done separately by both perinatologists without prior knowledge of the maternal or fetal clinical course or laboratory results. The 4-h period immediately before birth was scored by dividing the FHR record into 12 20-min epochs. These epochs were then combined into four hourly scores (−4 to −1 h) by summation. FHR scores (scaled 1 to 6: normal to abnormal) were assigned after evaluation of each 20 min epoch for specified fetal cardiotocographic features: baseline heart rate, variability, accelerations, decelerations (frequency, type, amplitude and duration), bradycardia, and sinusoidal pattern. These features were chosen because of their association with fetal oxygenation (Gimovsky & Cantis 1982; Hutson & Mueller-Heubach 1982). In addition to the individual hourly FHR scores, which were arbitrarily established to examine the temporal relation between Ep and FHR score, the overall mean hourly FHR score was also examined. This was derived for each subject by summing individual hourly FHR scores and dividing by the number of available hours. Since there was moderate agreement between the two judges' scoring of the FHR records, the average of their combined scores were utilized in the data analyses (see Appendix).

The condition and clinical history of the patient before delivery were recorded but were not used as entry or exclusion criteria. Four women were smokers, five had hypertension, and one had insulin-dependent diabetes mellitus. None had haemoglobin levels <10 g/dl during the pregnancy. Of the 41 women 24 (58%) were delivered by primary caesarean section.

In addition, the infant's sex, birthweight, gestational age, and 5-min Apgar score were recorded. Birthweight was adjusted for the variables of gestational age, sex, and birth order according to the method of Thomson *et al.* (1968) and expressed as a centile.

Cord blood was obtained at the time of delivery and maintained at 4°C as either mixed clotted or heparinized umbilical and/or artery whole blood for variable periods up to 2 days. We have previously demonstrated that storage of umblilical cord whole blood (with or without EDTA) for up to 4 days at 4°C or 21°C does not alter the results of plasma or serum Ep determinations. Moreover, we were unable to document any differences between simultaneous sampled umbilical artery and vein blood specimens (Widness *et al.* 1984). Ep was measured in duplicate plasma or serum cord samples using the double-antibody radioimmunoassay technique described by Garcia *et al.* (1979). With this assay, linear values are obtained between 5 and 100 mU/ml with appropriate dilutions made for those samples with higher concentrations; Garcia *et al.* (1982) have reported that heparinized plasma or clotted serum samples yield equivalent Ep results with an interassay coefficient of variation between 9 and 13%.

Analyses of results were done using the Statistical Package of the Social Sciences (SPSS) software and included use of analysis of variance

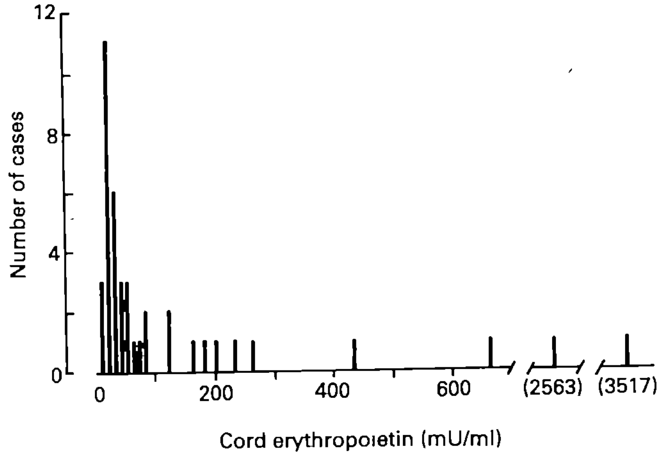

Fig. 1. Histogram of umbilical cord Ep levels in 10-mU/ml classes

(ANOVA), analysis of covariance (ANCOVA), correlation, multiple-regression, and path-model analysis.

Results

Cord plasma Ep concentration varied greatly with values ranging from 16 to 3517 mU/ml, (mean 235, median 42). When grouped by 10-mU/ml classes, the frequency pattern of the Ep values for the 41 newborn infants demonstrated a skewed distribution (skewness=4·30) with the modal class being 20–30 mU/ml (Fig. 1). To achieve a more normal distribution for data analysis purposes, Ep values were transformed first to their logarithms (log Ep=1·81±0·55 [mean±SD], skewness=1·58) and then to the logarithms of their logarithms (log.log Ep=0·24±0·12, skewness=0·98).

Due to uncontrollable clinical circumstances such as the variable duration of labour or physician intervention to effect delivery, the number of cases available for study through −4 h of labour before delivery declined from 41 to 31 (Table 1). Nonetheless, it was observed that the mean hourly FHR scores became increasingly abnormal as delivery approached (*F* ratio=4·65; d.f.=3, 143; $P<0{\cdot}01$ by one-way ANOVA). When mean hourly FHR scores were correlated with Ep (log.log) for each of the study hours before delivery, increasingly significant positive relations were observed in hours −1, −2, and −3 (Table 1) despite a decreasing number of available FHR records. During hour −4 when the number of cases dropped to 31, this correlation fell to borderline significance ($P<0{\cdot}06$). When the overall mean FHR scores for inclusive (−4 to −1) hours for all 41 subjects were used, a highly significant relation of Ep with FHR score was observed ($R=0{\cdot}53$, $P<0{\cdot}001$, Fig. 2).

Table 1. Correlation of hourly fetal heart rate (FHR) score with cord blood Ep (Log.Log)

Hour before delivery	Number of FHR records scored	Hourly FHR score*	Correlation coefficient (r)	*P* value
−4	31	8·6	0·343	<0·06
−3	36	9·1	0·55	<0·0003
−2	39	10·0	0·45	<0·04
−1	41	11·2	0·34	<0 03
Overall†	41	9·8	0·53	<0·001

* Mean score for the average of both judges
† Mean hourly score for hours −4 to −1 inclusive.

In an examination of the relation of FHR score with cord Ep, it was noted that elevated Ep levels were associated with infants with lower birthweight centiles. Therefore, ANCOVA was used to examine for potential interaction of birthweight and FHR score in the regression of Ep on FHR score. To do this, three birthweight classes (heavy, middle, and light) of approximately equal numbers ($n=13$–14) were created. No significant interaction was demonstrated justifying the use of all 41 birthweight centiles for multiple-regression analyses (Fig. 2).

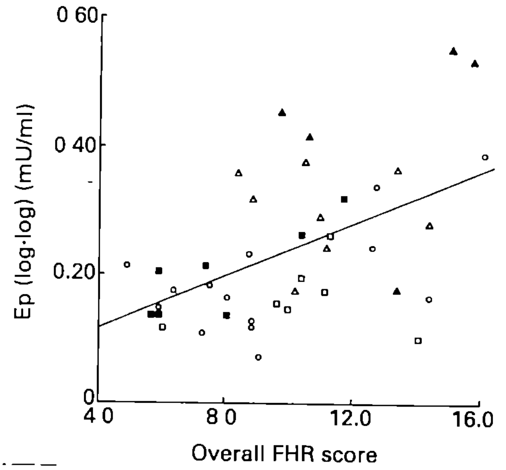

Fig. 2. Normal-weight-for-dates infants (between the 10th and 90th centile, $n=29$) are indicated by any of the open symbols (□, ○, or △). The three symbols represent each of the groupings used in the ANCOVA heavy (squares), middle (circles), and light (triangles). Light-for-dates infants (<10th centile) are indicated by the closed triangles (▲) ($n=5$) and the heavy-for-dates infants (>90th centile) by the closed squares (■) ($n=7$). $y=0{\cdot}021x+0{\cdot}031$; $r=0{\cdot}52$, $P<0{\cdot}001$

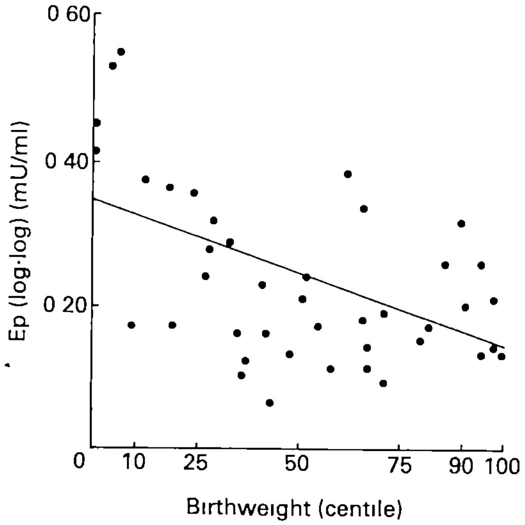

Fig. 3. Cord blood Ep (log log) versus birthweight centile $y=-0{\cdot}002x+0{\cdot}34$, $r=0{\cdot}52$, $P<0{\cdot}001$

The interrelation of Ep and FHR score with the clinical variables of birthweight centile was examined using simple and multiple-regression analyses. Using simple regression, cord Ep (log.log) correlated negatively with birthweight centile such that the lightest for gestational age fetuses had the highest plasma Ep levels ($r=-0{\cdot}56$, $P<0{\cdot}001$; Fig. 3). The value of the multiple r for Ep versus the combination of birthweight centile and FHR score as independent values was 0·63 with each contributing approximately equally in this relation (β: weights −0·37 and +0·40, respectively). The results of the individual correlation coefficients and β weights are shown in the path-analysis diagram (Fig. 4).

There was no difference in the cord Ep levels between the 24 infants born after labour and delivered by caesarean section and the 17 infants born vaginally. In addition, there was no association of Ep with gestational age It should be noted, however, that the spectrum of gestational age studied was narrow (mean 40·3, SD 2·0 weeks) with only three preterm (<37 weeks) infants included.

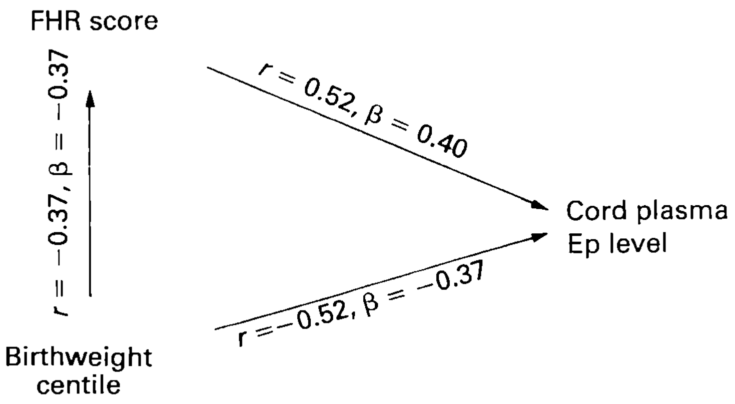

Fig. 4. Path-analysis diagram of relationship of FHR score and birthweight with cord Ep Correlation coefficients (r) and beta weights (β) are indicated

Discussion

Fetal cardiotocography is the most widely used clinical method for the assessment of fetal oxygenation during labour. In the present study it was found that the degree of abnormality noted on the FHR record during the 4 h before birth was significantly associated with the level of fetal plasma Ep measured at delivery. Since in animals Ep has been shown not to cross the placenta during late gestation, levels of fetal plasma Ep are indicative of fetal tissue oxygenation (Jacobsen *et al.* 1959; Zanjani & Gordon 1971).

In a previous study (Widness *et al.* 1984) we had found increased levels of Ep in fetal cord plasma after labour and speculated that it was due to fetal hypoxaemia induced by the stress of labour (Huch *et al.* 1977). In the present study, the lack of any relation of the mode of the delivery to fetal plasma Ep level is consistent with our hypoxaemia hypothesis. However, it must be noted that the present study was more selective since it predominantly emphasized those women with abnormal FHR records.

Intrapartum fetal hypoxaemic changes and fetal plasma Ep levels at delivery have not previously been compared in animals or in man. However, prepartum fetal hypoxaemia induced by a variety of means has been shown to result in increases in fetal plasma Ep in chronically catheterized sheep and goats (Zanjani & Gordon 1971; Philipps *et al* 1982; Widness *et al.* 1983). It is apparent from these studies that both the intensity and duration of hypoxaemia influence the appearance of an increase in Ep levels. Using fetal glucose infusion as a method of reducing fetal oxygen content, Philipps *et al* (1982) found that a 40–50% reduction in oxygen content was necessary before an increase in immunoreactive plasma Ep was noted. One explanation for this may be that compensatory physiological mechanisms (e.g., changes in heart rate, vascular resistance, blood flow distribution, haemoglobin oxygen affinity, etc.) are sufficient to avoid the critical level of tissue hypoxaemia necessary to raise plasma Ep levels. Similar compensatory changes may explain why 20 of the 41 (51%) fetuses in the present study had Ep levels within the range (9–41 mU/ml) that we had previously reported after apparently normal labour (Widness *et al.* 1984).

A second explanation for these findings is that the duration of fetal hypoxaemia necessary to produce a change in plasma Ep may have been insufficient given the relatively short duration of active labour. Studies in fetal animals indicate that several hours of hypoxaemia are necessary before plasma Ep levels rise (Zanjani & Gordon 1971; Widness *et al.* 1983). This period is similar to that observed in both in-vivo experiments in adult rats (Zanjani *et al.* 1971; Schooley & Mahlmann 1972) and in-vitro kidney perfusion studies in adult dogs (Erslev 1975). In these studies, the increase in Ep was shown to be secondary to the synthesis of new hormone rather than the release from stored pools. The temporal observation in the present study in which FHR abnormalities correlated best with cord Ep levels during hour −3 before birth is consistent with these reports in the literature. The poor correlation of Ep and FHR observed at hour −4 was likely due to the reduction in the number of subjects available for study and/or possible selection bias due to the delivery of the highest risk fetuses.

Of particular interest was the observation that light-for-dates infants had the highest plasma Ep levels. This finding is in agreement with our previous survey of a group of term infants with polycythaemia (vein haematocrit ≥65%) (Widness *et al.* 1982). In that study, light-for-dates polycythaemic newborn infants made up a disproportionately large number of those with elevated cord serum Ep levels. Two other studies have also reported a similar association of light-for-dates infants and elevated cord Ep levels (Finne 1968; Thomas *et al.* 1983). It is likely that many of these fetuses are marginally hypoxic before birth and, hence, may have elevated Ep levels during this period. Since in the present study Ep was studied only at delivery, information about possible dynamic changes of Ep concentration in the fetal plasma during labour could not be obtained.

The path statistical analysis diagram (Fig. 4) provides a speculative basis for summarizing the observations made in the present study. Each of the three outcome variables (cord Ep, FHR score and birthweight) may be affected by fetal tissue hypoxaemia. Since at present tissue hypoxaemia is impossible to quantify in the human fetus, the clinician must rely on other indirectly related but quantifiable parameters such as those used here: FHR pattern and intrauterine growth. As indicated by the direction of the arrows in the path-analysis diagram, low birthweight centile (which may be reflective of chronic fetal hypoxaemia) may influence both the FHR pattern as well as the fetal plasma Ep level. The β weights obtained in the multiple-regression analysis indicate that under the conditions of the study, FHR score and birthweight centile contribute approximately equally in predicting cord plasma Ep (+0·40 and −0·37, respectively). However, the multiple r value obtained for this relationship (r=0·63, Ep [log.log]=0·158+0·015 FHR score—0·0014 birthweight centile) indicates that the joint effect of these two variables is a better predictor of Ep than either taken alone.

Additional intrapartum studies in which plasma Ep is studied serially along with other simultaneously measured indicators of fetal oxygenation are needed. Based on the findings of the present study as well as data in the literature, the value of Ep estimations may lie in its potentially predictive value of moderately intense, sub-acute (hours) fetal hypoxaemia.

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Appendix

The degree of agreement between the two perinatal judges was assessed by an examination of the relation of one judge's FHR scores to the other's for each hour of study as well as for all 147 hours available for scoring (Appendix Table 1) When the difference between the FHR scores of both judges was plotted against the mean FHR score of both, there was no significant correlation indicating that the assumption of independence is not contradicted (Altman & Bland 1983) The bias between the two observers was found to be 0·68 scoring units (significantly different from zero. $t=-2{\cdot}78$, d f.=130, $P<0{\cdot}01$), and the estimate of error was 2 98 Although these features indicate a moderate degree of agreement between the two judges, there appeared to be some deviation from linearity, particularly with the lowest scores where the majority of data points were above the bias. To test for linearity, one judge's scores were classified into eight groups of increasing FHR scores. The correlation ratio (η) found using ANOVA was then compared with the correlation coefficient (r) of the linear plot It was found that the data were best described with a curvilinear plot (η=0·73 and r=0·66, F ratio for deviation from linearity=5·022 with d.f =6, $P<0{\cdot}0001$) This departure from linearity is the result of some disagreement between the two judges; however, it does not preclude the averaging of the two judges' scores for purposes of data analysis.

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Appendix Table 1. Correlation of hourly fetal heart rate (FHR) scores of both judges

Hour before delivery	Number of FHR records scored	FHR score*		Correlation coefficient	Standard error of estimation
		Judge X	Judge Y		
−4	31	8·7 (2·93)	8·4 (3 33)	0·64	2·53
−3	36	9·1 (3·24)	9·1 (3 78)	0·66	2 78
−2	39	10·4 (3·66)	9·7 (3·85)	0 75	2·54
−1	41	11 9 (3·14)	10 4 (3 94)	0·57	2·62
Total†	147	10·1 (3·47)	9·5 (3·78)	0·67	2·81

* Results are means (SD)

† Hours −4 to −1 inclusive

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Computerized histories facilitate patient care in a termination of pregnancy clinic: the use of a small computer to obtain and reproduce patient information

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Summary. An inexpensive microcomputer has been programmed to obtain histories from patients attending a pregnancy termination clinic. The system is nurse-interactive; yes/no and multiple-choice questions are answered on the visual display unit by a light pen. Proper nouns and discursive text are typed at the computer keyboard. A neatly formatted summary of the history is then provided by an interfaced printer. The history follows a branching pattern; of the 370 questions included in the program, only 68 are answered in the course of an average history. The program contains numerous error traps and the user may request explanations of questions which are not immediately understood. The system was designed to ensure that no factors of anaesthetic or medical importance would be overlooked in the busy out-patient clinic. The computer provides a much more complete history with an average of 42 more items of information than the pre-existing manual system. This system is demanding of nursing time and possible conversion to a patient-interactive system is discussed. A confidential questionnaire revealed a high degree of consumer acceptance.

A comprehensive and accurate history is a prerequisite of all good medical practice. There is a good chance of obtaining such a history in clinics, such as those for neurology, where each patient is interrogated in depth. The situation is less favourable when a faster tempo is required to process a large number of patients (Lilford *et al.* 1982). In gynaecological practice, $\geqslant 12$ patients are typically seen by one doctor during a single out-patient session. Thus the time allotted to patients requesting termination of pregnancy is often <20 min. During this time, the doctor would normally be expected to take the history, carry out the general and pelvic examination, perform the cervical smear and fill in numerous forms. As a result, little time remains to counsel the patient before she is admitted for operation. We have programmed a microcomputer to obtain the history from patients requesting termination of pregnancy. The questions were designed to provide the relevant medical and anaesthetic details and psychosocial background to facilitate further counselling. The system was assessed in a general gynaecology outpatient department.

Design of the system

General structure

A series of questions are displayed on the screen or visual display unit (VDU). The patient's answers are entered by an accompanying nurse using a 'light pen' or the computer keyboard. A summary of the history is then produced by a

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printer attached to the computer. This is scrutinized by the doctor before seeing the patient.

Equipment

The four items of hardware required are detailed in Table 1. The choice of microcomputers reflects our belief in their great potential for clinical data processing. The largest advantage is their low cost; the equipment required for this project can be obtained for £2000.

Software

The programs (software) are responsible for (a) implementation of the questionnaire by displaying a series of questions on the VDU; (b) forming the answers into strings of code for storage on the floppy disk; (c) 'writing' these strings to 'files' on the disk; (d) retrieving ('reading') the information from these files; and (e) printing a neat summary of the history on the basis of this coded information.

Because of the constraints on the memory capacity of the microcomputer itself, eight separate programs are required. These are stored on one of the disks and loaded onto the computer in a logical sequence once the system is activated. The process of loading a new program erases data already held in core memory (the memory of the CPU itself). These data are therefore recorded on a second floppy disk before each new program is obtained. Thus, by using a peripheral memory device, the limitation imposed by the size of core memory can be overcome. Access to patients' data is restricted by means of passwords which must be entered before a transcript of the history can be obtained. This protects the confidentiality of personal details held on disks. All programs were written in Basic.

The questionnaire

The conventional history is simulated by the use of a branching pattern whereby positive responses lead to more detailed questions on that topic Thus a history of rheumatic fever leads to questions about possible permanent cardiac damage and, if the response is positive, more detailed questions are asked with the possibility of even further branching. Of the 370 questions incorporated in the programs, only 68 are answered in the course of an average history. Most of the questions are of the fixed choice type ('closed' questions), which can be answered by 'yes', 'no' or 'do not know', or selected from a multiple-choice list ('menu'). Initially the nurse indicated the correct answer on the VDU by means of a light pen (Figs 1 and 2) but subsequently all programs were converted for keyboard entry. Open questions are reserved for proper nouns such as the names of people, places and rare diseases. These must always be entered on the computer keyboard. A provision is also made for the limited entry of unusual pertinent information in the form of unstructured narrative. The user is able to indicate when a question is not understood. A new display then appears with a more detailed explanation. Error traps are used to eliminate 'informal' errors. Such traps are designed to recognize illogical combinations, for example, if the patient is entered as 60 years old, the computer will restate the question, providing the user with an opportunity to correct this 'informal' error. Provision is also made to delete and replace 'formal' errors where the answer is logical but incorrect.

The questions dealing with the medical history follow a standardized pattern. Their main aim is to identify factors that could influence the safety of anaesthesia. Special prominence is therefore given to features such as allergies, bleeding disorders and recent steroid history. Any history of a previous medical disorder is explored in considerable detail.

The psychosocial background is aimed at identifying patients who may have an unfavour-

Table 1. Hardware requirements

Item	Manufacturer	Memory	Price (£s)
Computer	Commodore PET	30 kilobytes	800
Memory	8050 Commodore dual disk drive	800 kilobytes	800
Printer	3022 Commodore 80-column matrix printer (with programmable line-feed and tractor drive)	—	300
Light pen		—	60

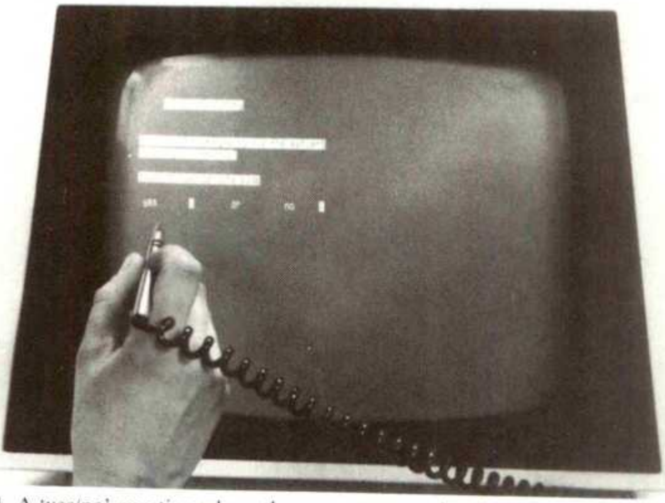


Fig. 1. A 'yes/no' question where the correct answer is selected by means of a light pen.

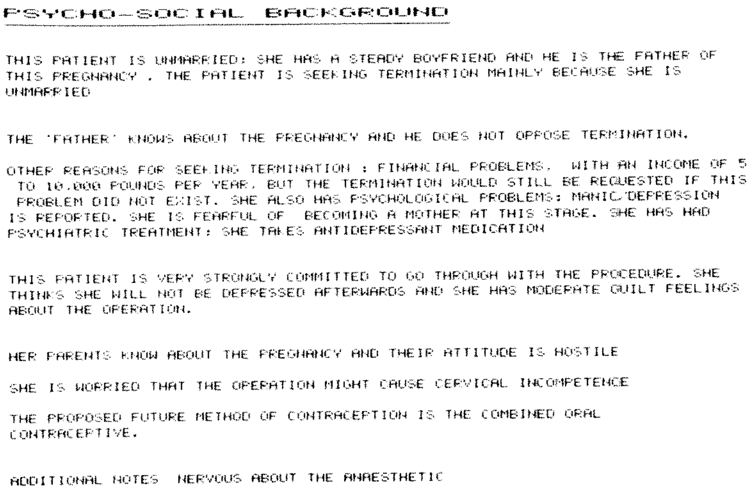
Fig. 2 The nurse entering the correct answer by means of a light pen.

able psychological reaction to the operation (Freeman *et al.* 1980; Robbins 1979; Shusterman 1979). Thus, after establishing the ostensible reason for the termination, questions are asked about the patient's previous mental health, the possibility of coercion and the patient's attitude towards abortion in general. The patient is also questioned on any specific fears she may have about the proposed operation and its sequelae. An example of the transcript which may result from this interview is shown in Fig. 3.

Production of the transcript

Early experience showed that the acceptability of the system in clinical practice depended not only on the quality of the history, but on the format of the transcript. Care was therefore taken to ensure that the doctor would assimilate the history easily and important positive and negative features are printed in larger typeface (Fig. 4). Initially, all answers were included in the transcript but later transcripts omitted negative responses to facilitate assimilation of histories. Although phrases like 'does not smoke' no longer appear in the transcript, clinicians used to the system were aware that the question had been asked and answered in the negative.

The transcript includes clinical advice based on some of the findings. Thus an 'action suggestion' reminds the doctor to perform a sickle test on patients whose families originated in West Africa (Fig. 5), or avoid thiopentone if there is a family history of porphyria.



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PSYCHO-SOCIAL BACKGROUND

THIS PATIENT IS UNMARRIED: SHE HAS A STEADY BOYFRIEND AND HE IS THE FATHER OF
THIS PREGNANCY . THE PATIENT IS SEEKING TERMINATION MAINLY BECAUSE SHE IS
UNMARRIED


THE 'FATHER' KNOWS ABOUT THE PREGNANCY AND HE DOES NOT OPPOSE TERMINATION.

OTHER REASONS FOR SEEKING TERMINATION : FINANCIAL PROBLEMS.  WITH AN INCOME OF 5
 TO 10,000 POUNDS PER YEAR. BUT THE TERMINATION WOULD STILL BE REQUESTED IF THIS
 PROBLEM DID NOT EXIST. SHE ALSO HAS PSYCHOLOGICAL PROBLEMS: MANIC/DEPRESSION
IS REPORTED. SHE IS FEARFUL OF  BECOMING A MOTHER AT THIS STAGE. SHE HAS HAD
PSYCHIATRIC TREATMENT: SHE TAKES ANTIDEPRESSANT MEDICATION


THIS PATIENT IS VERY STRONGLY COMMITTED TO GO THROUGH WITH THE PROCEDURE. SHE
THINKS SHE WILL NOT BE DEPRESSED AFTERWARDS AND SHE HAS MODERATE GUILT FEELINGS
ABOUT THE OPERATION.

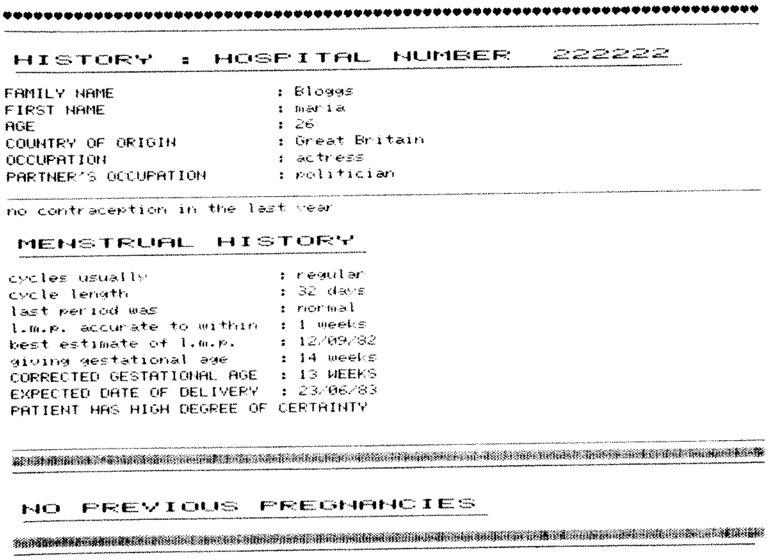

HER PARENTS KNOW ABOUT THE PREGNANCY AND THEIR ATTITUDE IS HOSTILE

SHE IS WORRIED THAT THE OPERATION MIGHT CAUSE CERVICAL INCOMPETENCE

THE PROPOSED FUTURE METHOD OF CONTRACEPTION IS THE COMBINED ORAL
CONTRACEPTIVE.


ADDITIONAL NOTES  NERVOUS ABOUT THE ANAESTHETIC
```

Fig. 3. An example of the psychosocial history which is produced by the computer program. With the exception of the last item, all the above information was obtained by an answer to 'closed' questions, i.e. 'yes/no' or a number.



```
HISTORY : HOSPITAL NUMBER  222222

FAMILY NAME                   : Bloggs
FIRST NAME                    : maria
AGE                           : 26
COUNTRY OF ORIGIN             : Great Britain
OCCUPATION                    : actress
PARTNER'S OCCUPATION          : politician

no contraception in the last year

MENSTRUAL HISTORY

cycles usually                : regular
cycle length                  : 32 days
last period was               : normal
l.m.p. accurate to within     : 1 weeks
best estimate of l.m.p.       : 12/09/82
giving gestational age        : 14 weeks
CORRECTED GESTATIONAL AGE     : 13 WEEKS
EXPECTED DATE OF DELIVERY     : 23/06/83
PATIENT HAS HIGH DEGREE OF CERTAINTY


NO PREVIOUS PREGNANCIES
```

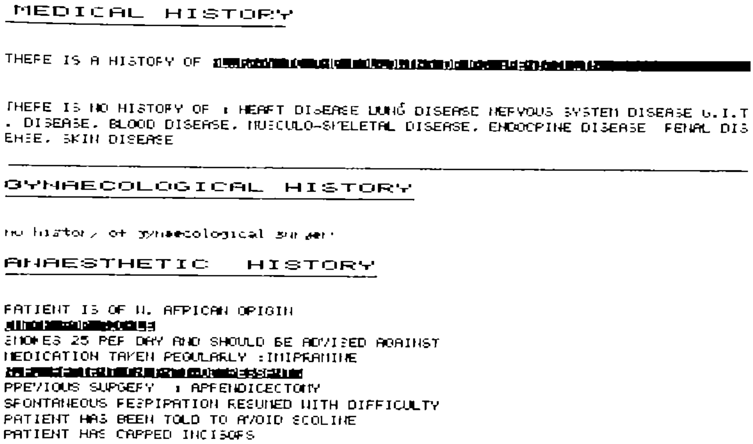
Fig. 4. The initial portion of a computerized patient history.

Administrative functions

The initial acceptance of computerized systems in clinical practice depends not only on the production of a complete history, but also on saving money and effort. Furthermore, there are many time-consuming administrative tasks which are eminently suitable for mechanisation. Thus in addition to the automatic transcript of the patient's history, the system produces a letter to the general practitioner in which the history is summarized. The doctor may, if he wishes, add further comments by hand before signing this letter.

Assessment

The system was introduced on an experimental basis in a busy out-patients clinic, and 100 patients have been interviewed. The following detailed observations were made on the first 40 patients who were seen before the establishment of a day-care termination of pregnancy service at St Bartholomew's Hospital. (a) Time: the time taken to obtain each history is measured automatically by the computer. This was compared with the average time required by four different registrars to take similar histories. (b) User reactions: an anonymous confidential questionnaire



```
MEDICAL HISTORY

THERE IS A HISTORY OF [redacted]

THERE IS NO HISTORY OF : HEART DISEASE LUNG DISEASE NERVOUS SYSTEM DISEASE G.I.T
. DISEASE. BLOOD DISEASE. MUSCULO-SKELETAL DISEASE. ENDOCRINE DISEASE  RENAL DIS
EASE. SKIN DISEASE

GYNAECOLOGICAL HISTORY

no history of gynaecological surgery

ANAESTHETIC HISTORY

PATIENT IS OF N. AFRICAN ORIGIN
[redacted]
SMOKES 25 PER DAY AND SHOULD BE ADVISED AGAINST
MEDICATION TAKEN REGULARLY :IMIPRAMINE
[redacted]
PREVIOUS SURGERY  : APPENDICECTOMY
SPONTANEOUS RESPIRATION RESUMED WITH DIFFICULTY
PATIENT HAS BEEN TOLD TO AVOID SCOLINE
PATIENT HAS CAPPED INCISORS
```

Fig. 5. The 'anaesthetic' history, including relevant action suggestions

was handed to 40 consecutive patients after the interview. This was completed by the patient and returned in a plain envelope as they left the clinic. (c) Quality assessment: the histories of 40 consecutive and completely unselected patients who had been seen by the clinical registrar and clerked by the admitting senior house officer were compared with the first 40 computer histories. The total amount of information obtained by each method (registrar *plus* house officer versus computer) was quantified. In addition, the number of items of anaesthetic, gynaecological, general and psychosocial interest were enumerated (anaesthetic information included any serious medical disorder; gynaecological included the menstrual and contraceptive history and details of previous pregnancies or gynaecological surgery).

Results

Time

The time taken to obtain the computerized histories averaged 17 min (range 10 to 27). This compared with an average time of 4 min required by the registrar in the clinic.

User reactions

Detailed consumer attitudes are shown in Table 2. There were no serious objections on the part of patients or staff. Of the patients questioned 95% enjoyed the exercise, and 97% thought it was a good idea. A formal staff reaction survey was not conducted. The three members of the nursing staff most involved in the project were initially enthusiastic about the computer interview, but once the day-care termination of pregnancy service was fully operational, the time required to obtain the exhaustive computer history became a constraint. As they became more experienced with the computer system, these users all expressed a clear preference for keyboard entry over the light-pen method. The latter, while superficially attractive, was more difficult to use and more distracting than simple 'yes', 'no' or number responses on the computer keyboard.

Table 2. Consumer response to confidential questionnaire—40 patients

	Yes	No	Don't know
Did you enjoy having your history taken by computer?	38	—	2
In your opinion, did the computer take a more detailed history than most doctors?	27	11	2
Do you think the computer history is a good idea?	39	1	—
Did you find the system impersonal or unfriendly?	1	39	—

Quality comparison

The computer obtained an average of 41·9 more items than the manual history (Table 3). This improvement was found in the gynaecological, medical and psychological components of the history but was most noticeable in the latter.

Discussion

In the present study, we elected to employ a member of the nursing staff to enter the answers, although a direct patient/computer system could have been designed. Such systems use specially adapted 'yes/no' or multiple-choice keyboards and cannot therefore accept proper nouns, such as the name of a hospital, rare disease or unusual drug (Lilford *et al.* 1983*b*; Lucas *et al.* 1977).

The advantages of this computerized system are discussed below.

Production of a complete history with no omissions

The ability of our system to provide more detailed information has been amply demonstrated. A cross-over study comparing the amount of information obtained from each patient by both methods would have provided a more accurate comparison, but this would have imposed an additional strain on patients who, given the nature of the clinic, were already under considerable stress. Such a study has, however, been conducted in antenatal care and in gynaecology (Lilford *et al.* 1983*a, b*). The results confirm that considerably more information is provided by computerized questionnaires than by conventional manual systems. It could also be argued that many of the deficiencies in the manual records may have resulted from a failure to record details which had been elicited. However, this is unlikely to have accounted for the observed shortfall in recorded information. Computerized notes form a complete, well-structured, neatly formatted record which facilitates communication within the hospital.

A complete history with no omissions is a feature of all questionnaire-based systems as they avoid the limitations of human memory. Studies comparing the amount of information by questionnaires (manual or computer-based) with that obtained by conventional methods show that questionnaires provide more information (Chodoff & Gianaris 1973; Chun *et al.* 1976; Grosssman *et al.* 1971) and that a proportion of the additional details are of practical clinical value (Lilford *et al.* 1982, 1983*a*; Grossman *et al.* 1971). Computers have the great advantage over manual questionnaires of being able to accommodate complex branching patterns which would require much paper handling in a manual questionnaire.

Enabling the physician to make more effective use of his time

Without this system, routine history-taking encroaches on time which could otherwise be spent in counselling patients in much greater detail than was previously possible. Furthermore, the nursing staff carrying out the interview, whose previous role was essentially administrative, became more involved in the medical aspects of the clinic. Initially this was much appreciated, but once the day-care service was fully established and the number of termination requests quadrupled, the time required to complete the computer interview became an obstacle. Direct patient interactive systems have much to offer in this regard.

Providing clinical reminders

Important features are highlighted in larger typeface and, where appropriate, an action suggestion appears. Thus if a patient is a Negro or of

Table 3. Comparison of amount of information obtained by computerized and manual questionnaires

Type of information	Manual Mean (range)	Computerized Mean (range)	Mann-Whitney significance test
Relevant to anaesthesia	5·9 (1–13)	16·6 (11–37)	$P<0{\cdot}0001$
Psychosocial importance	2 5 (0–11)	18·7 (14–25)	$P<0{\cdot}0001$
Gynaecological	6·9 (2–11)	17·3 (9–42)	$P<0{\cdot}0001$
Present complaints and miscellaneous	6·2 (1–14)	10·8 (10–13)	$P<0{\cdot}0001$
Total	21·5	63·4	

West African descent, the doctor is reminded to perform a sickle test. The disruption caused by admission of a patient without this result is therefore avoided. Similarly, a routine check list reminds the doctor to ascertain the need for rhesus prophylaxis. Some have suggested that action suggestions pre-empt the functions of a physician, but observations of clinical practice (and malpractice claims) overwhelmingly support their use. The human mind cannot perform memory-based tasks with absolute efficiency (Bulpitt *et al.* 1976) and the staff of teaching hospitals characteristically omit 20% of tests indicated by the criteria of their unit (Anderson *et al.* 1976). Some 50% of all new cases of rhesus disease in the UK are the result, not of natural immunization during pregnancy, but of failure to administer anti-D prophylaxis after miscarriage or ectopic pregnancy (Tovey *et al.* 1978). The scope for such errors of omission can only become greater as medicine advances and the number of possible investigations increases. Computerized reminders can therefore be regarded as a form of quality control for medical practice (McDonald 1976).

Research

Computerized notes provide a large and almost infinitely expandable data base of rapidly retrievable information. At one stage, our system was made to exploit yet another of the facilities offered by the computer; that of generating random numbers. Though not directly relevant to the main project, we had planned to allocate patients to treatment and control groups in a trial of the efficacy of vaginal prostaglandins, on this basis. This study was interrupted by the departure of the principal investigators (P.B. and R.J.L.).

Despite the above advantages, misgivings are often expressed that computerized notes are impersonal and a threat to medical confidentiality. These criticisms have been repudiated elsewhere (Lilford & Chard 1981), but it cannot be too strongly emphasised that obtaining the history by computer does not diminish the time that doctors can spend with their patients and that, if anything, more time is made available for unstructured dialogue. The acceptability of computerized notes is reflected in our own and numerous other consumer attitude studies (Grossman *et al.* 1981; Dove *et al.* 1977; Slack & Van Cura 1968). The computerized history does however, take longer to obtain. It imposes a new discipline on medical staff. The history cannot be shortened or accelerated towards the end of a long clinic. Thus staff acceptance cannot be taken for granted despite the clear-cut and demonstrable advantages of this method Many years may be required before patient/staff interactive history systems become the rule. Such systems are likely to succeed where highly structured history forms are already filled in by medical staff e.g. antenatal care. Direct patient-answered systems may prove more acceptable for many other purposes as these do not have implications for staffing levels.

The system described does not pose a threat to medical secrecy. The printed transcript becomes part of the patient's hospital folder. Data held on disk are retained within the department and are not accessible to any centralized data bank. These files are further protected by means of passwords.

In conclusion, we have implemented a system which not only provides comprehensive data collection and clinical advice, but also emphasizes the psychological aspects of medical care. This permits a better service to patients and, by reminding the medical staff of points which might otherwise be forgotten, it also has an educational function and the nursing attendant is permitted to interact with the patient on a more personal basis.

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α-Fetoprotein elevation and proteinuric pre-eclampsia

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Summary. In a retrospective study of pregnancy complicated by unexplained elevation of maternal serum α-fetoprotein (AFP), 60 patients were compared with 120 control subjects. Proteinuric pre-eclampsia occurred in 13% of the study patients compared with 1% of the control subjects. Primiparity, previous mid-trimester abortion and recurrent abortions were also significantly more common in the study group. It is proposed that an abnormality of the placenta predisposes to complications and that this abnormality is expressed early in pregnancy when the AFP level is first measured. This group of women is at high risk of adverse pregnancy outcome and requires careful monitoring.

Maternal serum α-fetoprotein (AFP) estimation at 15–18 weeks gestation is used as a screening test for the presence of fetal neural-tube defect (NTD). For this purpose, however, the test lacks specificity and many women who are identified with high serum AFP levels will be found after ultrasound and amniocentesis, to have a fetus without NTD. It has become apparent that the pregnancy outcome in these women is often abnormal. Because we recently treated several women with severe pre-eclampsia whose AFP levels were elevated without apparent cause, we have performed a retrospective case–control study to document hypertensive complications of pregnancy in such women.

Patients and methods

AFP screening is routinely performed at Queen Charlotte's Maternity Hospital between 16 and 18 weeks gestation. Serum AFP was measured by single antibody radioimmunoassay and values which exceeded three times the median level (MoM) for singleton pregnancies of the same gestational age were regarded as abnormally high. In 1982, of 3470 women screened 89 had a high serum AFP level. Of these eight (9%) had a fetus with NTD, 14 (16%) had twins and seven (8%) had abortions within 2 weeks of the blood test. The remaining 60 women were considered to have unexplained AFP elevation and they are the subjects of this report.

All women had gestational age confirmed by early ultrasound. Twenty-nine had amniocentesis to exclude NTD and 31 either had a normal AFP level on repeat testing (29) or refused amniocentesis (2). Two controls were chosen for each study patient These were the women whose blood samples were received in the laboratory immediately before and after the study patients' and whose AFP levels were normal.

All case records were examined by V S. or T.L. Where information was lacking, the patient herself or her general practitioner was contacted.

We used the criteria of the American College of Obstetricians and Gynecologists (ACOG) (Hughes 1972) for the diagnoses of pre-eclampsia, superimposed pre-eclampsia, chronic hypertension and gestational hypertension. We included a further category of proteinuric pre-eclampsia which refers to those women who also had significant proteinuria. This was defined as >300 mg protein/litre in 24-h collection or mid-stream urine specimen or one + or greater on urine testing with Albustix (at least twice). We modified the ACOG criteria

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slightly such that we required a blood pressure of 140/90 mmHg twice to be designated hypertension. We required a rise in systolic blood pressure of ≥30 mmHg or a rise in diastolic blood pressure of ≥15 mmHg over the booking blood pressure (before 20 weeks) in addition to hypertension described above for the diagnosis of pre-eclampsia.

For those without proteinuria we required significant oedema (i.e. facial and finger swelling noted in antenatal record) for the diagnosis of pre-eclampsia.

Birthweight centiles were allocated using standard tables (Milner & Richards 1974). Statistical comparison was by means of the χ^2 test with Yates correction.

Results

The control and study groups were comparable in mean age (28·6 and 29·1 years). Their previous obstetric history is summarized in Table 1. There was a significantly higher proportion of primiparous women and of previous miscarriage in the study group. In particular, mid-trimester abortion and recurrent abortion (three or more spontaneous abortions) were significantly more frequent.

Table 1. Past obstetric history in women with high and normal serum α-fetoprotein AFP levels

Obstetric history	Study group (n = 60)	Control group (n = 120)	P
Parity			
0	34 (57)	42 (35)	<0·01
≥1	26 (43)	78 (65)	
Abortions			
First trimester	16 (27)	21 (18)	NS
Second trimester	6 (10)	2 (2)	<0·05
Recurrent	6 (10)	0	<0·01

The figures in parentheses represent the percentage of women in each group.

In the index pregnancy, threatened abortion complicated 14 pregnancies in the study group and three in the control group ($P<0{\cdot}01$). In the study group 16 women were delivered before 37 weeks, five of them had delivery induced because of pre-eclampsia and the other 11 laboured spontaneously, seven women were delivered before 34 weeks. Only three women in the control group were delivered before 37 weeks ($P<0{\cdot}01$).

There were 16 hypertensive patients in each group and these were analysed in further detail (see Table 2). Chronic hypertension was present in a similar proportion of women in each group. It is in the incidence of superimposed and *de novo* proteinuric pre-eclampsia that the study group exceeds the control group. All eight patients with proteinuric pre-eclampsia in the study group were primiparous and six of them were delivered at or before 36 weeks.

There were no fetal losses in the control group, and only one baby with congenital abnormality, a cleft palate. In the study group, there were two mid-trimester abortions and one neonatal death. Low birthweight (<2500 g) was found in 17 babies in the study group and in five babies in the control group ($P<0{\cdot}01$) Of the 17 low-birthweight babies in the study group, eight were associated with pre-eclamptic pregnancies. Although a birthweight of less than the 10th centile was more than twice as prevalent in the study group (14% versus 6%) the difference was not statistically significant.

Table 2. Classification of pregnancy hypertension in women with high and normal serum AFP levels

	Study group (n = 60)	Control group (n = 120)	P
No hypertension	44 (73)	104 (87)	
Gestational hypertension	3	2	NS
Pre-eclampsia	2	2	NS
Chronic hypertension (CHT)	3 (5)	9 (7·5)	NS
Chronic hypertension with superimposed pre-eclampsia	0	2	NS
Proteinuric pre-eclampsia (A)	5	1	<0·05
CHT with superimposed proteinuric pre-eclampsia (B)	3	0	NS
Total proteinuric pre-eclampsia (A+B)	8 (13)	1 (1)	<0·01

The figures in parentheses represent the percentage of women in each group.

Discussion

The value of antenatal screening by means of maternal serum AFP estimation in the detection of open NTD is undisputed. However, the results of this test can also be abnormal in pregnancies with other fetal abnormalities (Clarke *et al.* 1977), congenital nephrosis (Kjessler *et al.* 1975), multiple pregnancy, impending abortion or fetal death *in utero* (Seppala & Ruoslahti 1973). These can often be diagnosed clinically or by ultrasound, leaving a group with elevated serum AFP levels which are unexplained. This abnormality has also been associated with remote complications such as low birthweight and increased perinatal mortality (Persson *et al.* 1983). We have confirmed these findings in addition to certain other abnormalities of pregnancy in these women, not previously described

We found a higher incidence of proteinuric pre-eclampsia in the study group. This complication only occurred in primiparous women, eight of 34 primiparae in the study group and one of 42 primiparae in the control group. In accord with this finding is a recent retrospective study of 24 women with proteinuric pre-eclampsia (Moore & Redman 1983). A history of high serum AFP in early pregnancy in these patients was more common (12·5%) than in a matched control group (0%). In our two groups the prevalence of chronic hypertension was similar, but more women in the study group developed superimposed proteinuric pre-eclampsia

AFP has also been measured in late pregnancy. In a study of hypertensive women in the third trimester, AFP levels were found to be significantly higher than in non-hypertensive controls, (Clayton-Hopkins *et al.* 1982). The values in patients with pre-eclampsia were higher than in those with chronic hypertension. Higher levels were also found with fetal distress in 'toxaemia' of pregnancy (Garoff & Seppala 1976).

Attention has been drawn to the association of low birthweight (<2500 g) with high maternal AFP level (Brock *et al.* 1977, Smith 1980) and our findings are in agreement. In addition, we found that nearly 50% of the low-birthweight babies were associated with pre-eclamptic pregnancies.

In contrast to a recent study (Persson *et al.* 1983) we did not find that previous spontaneous first-trimester abortion was more common in the study group, but a history of mid-trimester or recurrent abortions was significantly more common. This association has not been reported before and suggests a recurring placental abnormality.

The mode of entry of AFP from the fetal to the maternal circulation is not established. Normally there is a concentration gradient for AFP of approximately 10 000 multiples between the two circulations (Brock 1979). There must, therefore, be a barrier to the transfer of this protein across the placenta in normal pregnancy which is defective in some cases as described here.

It is improbable that amniocentesis itself predisposed to the complications described. Six of the hypertensive pregnancies, both the abortions and five of the low-birthweight infants occurred in patients who did not have an amniocentesis. Other studies have shown the relative safety of amniocentesis (Philip & Bang 1978; Read *et al.* 1980).

Thus, we have described a group of women with late pregnancy complications and in particular proteinuric pre-eclampsia, in whom an abnormality was detectable in early pregnancy An understanding of the nature of the defect that leads to elevation of the maternal serum AFP in these patients may widen our understanding of the development of pre-eclampsia and other pregnancy complications.

We believe that unexplained elevation of AFP at screening in early pregnancy is an indicator of high risk for that pregnancy and that all such women should be monitored closely. In fact in the population studied, AFP elevation indicated a higher risk of other complications than of NTD. Moreover, the obstetrician should not be reassured by a repeat estimation which gives a normal result; in 22 of the women studied a repeat AFP level had been normal. One-third of these women also suffered pregnancy complications and three of the eight patients with proteinuric pre-eclampsia came from their number

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Maternal plasma prostaglandin E_2 metabolite levels during human pregnancy and parturition

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Summary. Because of methodological problems associated with the measurement in biological fluids of both prostaglandin E_2 (PGE_2) and its unstable principal circulating metabolite 13,14-dihydro-15-keto-PGE_2 (PGEM), there is little reliable information on these prostaglandins in human pregnancy and parturition. The recent discovery of a stable PGEM degradation product 11-deoxy-13,14-dihydro-15-keto-11β,16ε-cyclo-PGE_2 (bicyclo-PGEM) has provided a means of studying endogenous plasma levels of PGEM which circumvents the problems encountered with direct measurements of PGE_2 and PGEM. Using a radioimmunoassay for bicyclo-PGEM we have therefore determined maternal peripheral plasma PGE_2 metabolite levels during human gestation. PGE_2 metabolite levels did not alter significantly during the second or third trimesters nor during labour. This contrasts with maternal peripheral plasma levels of the principal circulating metabolite of $PGF_{2\alpha}$ 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM) which increases several fold during labour. Compared to PGE_2 therefore, $PGF_{2\alpha}$ may be quantitatively the more significant prostaglandin associated with human parturition.

That endogenous prostaglandins play important roles in human pregnancy and parturition is undoubted (Turnbull 1983), but which prostaglandins from what tissues act where and when and how and to what effect remains a fertile area of research.

Thus while the uterotonic and cervical ripening pharmacological effects of exogenous prostaglandin E_2 (PGE_2) and $PGF_{2\alpha}$ during human gestation are well documented (Embrey 1981), the relative physiological contributions that endogenous production of these two primary prostaglandins make to the various processes of normal pregnancy and parturition are less well defined. It is unclear for example whether both these prostaglandins are natural mediators of both uterine contractions and cervical ripening, or whether their functions and predominant sites of action differ. Such matters merit investigation, for knowledge of physiological mechanisms provides a basis for understanding pathological processes and developing rational therapies.

Answering these questions is hampered by methodological difficulties associated with the measurement of prostaglandin concentrations in tissues and body fluids, especially blood. Thus low endogenous concentrations, chemical instability, short half-lives and artifactual alterations of levels during sampling and storage complicate attempts to estimate reliably plasma concentrations of primary prostaglandins (Smith *et al.* 1973; Jubiz & Frailey 1974). Although plasma levels of hormone and their metabolites are determined by a dynamic interplay between rates of entry into and exit from the plasma compartment, because prostaglandin metabolites are rapidly formed following the synthesis and liberation of the primary prostaglandins (Ferreira

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& Vane 1967), the production and release of primary prostaglandins is in general the major determinant of plasma prostaglandin metabolite levels. In-vivo studies demonstrating close parallelism between primary prostaglandin levels and corresponding plasma prostaglandin metabolite concentrations (Granstrom & Kindahl 1976; Mitchell *et al.* 1976; Demers *et al.* 1983) support this contention. Moreover, prostaglandin metabolites not only reflect output of the parent prostaglandin but in comparison they are also generally more stable, have longer half-lives, circulate in higher concentrations and are less susceptible to sampling and storage artifact. It has been recommended therefore that peripheral plasma prostaglandin measurements be of the main metabolite forms of the primary prostaglandins (Granstrom & Samuelsson 1978).

While such a methodological strategy has proven to be both possible and useful for $PGF_{2\alpha}$ in terms of 13,14-dihydro-15-keto-$PGF_{2\alpha}$ (PGFM) (Granstrom & Kindahl 1976; Mitchell *et al.* 1976), it has not been successful for PGE_2 because its metabolite 13,14-dihydro-15-keto-PGE_2 (PGEM) is itself unstable. Thus early reports of either peripheral plasma PGE_2 or PGEM in human pregnancy and parturition must be viewed with circumspection. But the recent discovery of a stable PGEM degradation product 11-deoxy-13,14-dihydro-15-keto-11β,16ε-cyclo-PGE_2 (bicyclo-PGEM) (Fitzpatrick *et al.* 1980; Granstrom *et al.* 1980) has identified a compound suitable for assay (Bothwell *et al.* 1982), thereby providing a potential means to acquire reliable knowledge of the in-vivo role(s) of PGE_2 during human gestation.

This study reports maternal peripheral plasma PGE_2 metabolite concentrations (measured in terms of bicyclo-PGEM) in a serial set of samples collected during human pregnancy and parturition and in a cross-sectional set of samples collected during the progression of labour.

Subjects and methods

Serial blood samples were obtained from 12 women at monthly intervals during their second and third trimesters, at term (38–42 weeks gestation) and during established labour. Blood samples were obtained from a further 36 women either at term and not in labour (n=9), in early labour with cervical dilatation <5 cm (n=12) or in late labour with cervical dilatation ⩾5 cm (n=15). All the women in early labour were delivered within 6 h of sampling and those in late labour within 3 h of sampling. Cervical dilatation was determined by vaginal examination after blood sampling. No patient had epidural analgesia at the time of sampling. Sample results of women in labour given parenteral analgesia (intramuscular pethidine hydrochloride with or without the antiemetic promethazine hydrochloride) before sampling (11/39) were not significantly different from the results of those without analgesia (28/39) and so have been included in the analyses. All subjects were healthy with no past or current history of serious or chronic illness. They were of mixed parity. Each pregnancy was clinically normal and each labour began spontaneously at term, progressed without complication, did not require oxytocic augmentation and resulted in the spontaneous vaginal delivery of a singleton healthy infant. No patient admitted to a recent intake of steroidal drugs or non-steroidal anti-inflammatory medications. Samples were obtained with the consent of the subjects and the approval of the local ethics committee.

Samples

Blood samples were collected by antecubital venepuncture into plastic tubes on ice containing ethylene diamine tetra-acetic acid and centrifuged within 30 min of collection at 1000 ***g*** and 10°C for 15 min. Each plasma sample was divided into two parts which were stored at −20°C until assayed.

Assays

Plasma bicyclo-PGEM and PGFM concentrations were measured in different portions of the same sample using sensitive, specific radioimmunoassays fully described elsewhere (Demers *et al.* 1983; Mitchell *et al.* 1978*a*, *b*).

Statistics

Statistical evaluation of results utilized the Mann–Whitney rank sum test.

Results

Mean serial maternal plasma bicyclo-PGEM levels during pregnancy did not change significantly before or with the onset of labour (Fig. 1). Furthermore although PGFM levels rose

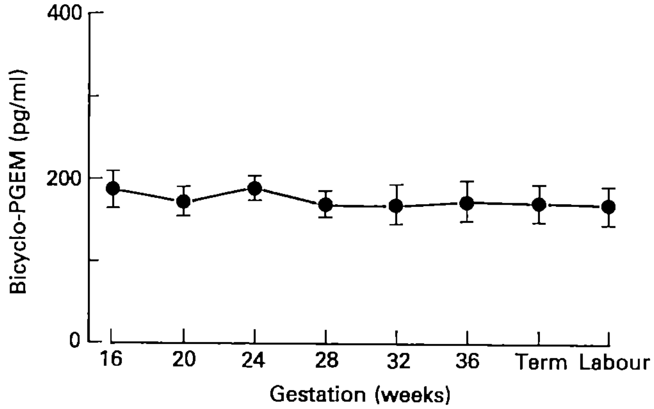

Fig. 1. Serial ($n=12$) maternal peripheral plasma prostaglandin E_2 metabolite (bicyclo-PGEM) concentrations (mean ±SEM) during human pregnancy and labour.

significantly ($P<0.01$), no change in bicyclo-PGEM levels was detected during the progression of labour (Fig. 2).

Discussion

The rise in maternal peripheral plasma PGFM concentrations during labour observed in this study agrees with previously published data (Green *et al.* 1974; Mitchell *et al.* 1978*a*) and supports an acute role (most probably uterotonic) for $PGF_{2\alpha}$ in the events of parturition.

The lack of any significant change in maternal peripheral plasma PGE_2 metabolite concentrations during pregnancy and parturition is interesting.

In the absence of any confounding information on PGE_2 metabolite excretion in human pregnancy and given that enzymatic activities of studied prostaglandin metabolizing systems do not appear to alter during human gestation (Keirse *et al.* 1976; Falkay *et al.* 1980; Jarabak 1980), it may reasonably be assumed that a close parallelism exists between PGE_2 production and plasma PGE_2 metabolite levels in the pregnant woman. There would appear therefore to be no quantitatively significant increase in maternal PGE_2 production during pregnancy or parturition in so far as detection in terms of peripheral plasma metabolite levels is concerned.

This finding suggests that during labour prostaglandin endoperoxide metabolism may be specifically directed more toward $PGF_{2\alpha}$ than toward PGE_2 at least in some maternal tissues such as myometrium. A recent in-vitro study of human intrauterine tissue prostaglandin concentrations supports this possibility (Satoh *et al.* 1981).

Such a modulation of prostaglandin production could be achieved by several mechanisms including alterations in precursor free arachidonic acid concentrations, qualitative and/or quantitative variations in prostaglandin synthesis cofactors and/or manipulation of the activity of 9-keto-reductase conversion of PGE_2 to $PGF_{2\alpha}$ (Flower *et al.* 1973; Jarabak 1980).

Although the data of this study suggest that

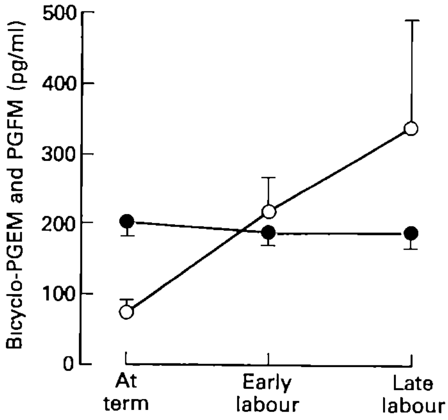

Fig. 2. Maternal peripheral plasma prostaglandin E_2 metabolite (bicyclo-PGEM) (●) and prostaglandin $F_{2\alpha}$ metabolite (PGFM) (○) concentrations (mean ±SEM) in women at term ($n=9$), during early labour (cervical dilatation <5 cm) ($n=12$) and during late labour (cervical dilatation ≥5 cm) ($n=15$).

$PGF_{2\alpha}$ is quantitively more important than PGE_2 during human parturition, the human myometrium and cervix at term are several fold more sensitive to PGE_2 than to $PGF_{2\alpha}$ (Embrey 1969; Mackenzie & Embrey 1979). Moreover amniotic fluid PGE_2 levels increase with labour albeit less dramatically than amniotic fluid $PGF_{2\alpha}$ concentrations (Keirse *et al.* 1974; Dray & Frydman 1976) and so too do umbilical vein plasma PGE_2 levels (Bibby *et al.* 1979). It therefore remains possible that some degree of enhanced local uterine or fetal PGE_2 production, undetectable in terms of increased maternal peripheral plasma PGE_2 metabolite levels, may exert significant effects in relation to human labour.

Studies of prostaglandin receptor populations in pregnant human intrauterine tissues may help further to clarify the association between the findings of this study and the disposition of in-vivo roles for endogenous prostaglandins during human gestation.

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Cimetidine in labour: absence of adverse effect on the high-risk fetus

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Summary. In a prospective randomized trial, 36 women received cimetidine and 32 magnesium trisilicate mixture BP as antacid therapy every 2 h in labour. The women belonged to a high-risk category and the infants born were <36 weeks gestation, or <2000 g birthweight or otherwise in jeopardy because of severe maternal pre-eclampsia or diabetes. Measurements of a wide range of haematological and biochemical variables revealed no differences between the two groups of babies. The frequency of complications found in the infants was similar, although infants born to the women who received magnesium trisilicate required oxygen therapy for a longer period. Cimetidine did not appear to affect the development of gastric acidity, or to increase bacterial colonization of the gastrointestinal tract in the infant.

Routine alkali therapy is widely prescribed for women in labour as prophylaxis against acid-aspiration pneumonitis Alkalis will, however, increase the volume of the gastric contents, and particles in emulsion alkalis may themselves cause lung damage if inhaled (Kuchling *et al.* 1975; Gibbs *et al.* 1979; Eyler *et al.* 1982). Hydrogen-receptor blocking agents present an alternative method of reducing gastric acidity without increasing volume—they do, however, cross the placental barrier although no adverse effects have been reported following their use in labour (Howe *et al.* 1981; Johnston *et al.* 1983; Hodgkinson *et al.* 1983; McAuley *et al* 1983). Infants already at risk because of placental dysfunction or prematurity would, however, be more susceptible to untoward drug effects and hence a detailed study of such babies might reveal side-effects not apparent in full-term healthy infants. This paper reports the findings of a prospective randomized trial comparing a group of high-risk babies whose mothers had received cimetidine during labour with a similar group whose mothers had conventional oral alkali therapy.

Patients and methods

The women were identified on admission to the labour ward and three main categories were selected: (i) premature labour i.e. <36 weeks gestation; (ii) intrauterine growth retardation, estimated fetal weight <2000 g; (iii) other conditions such as severe pre-eclampsia and diabetes. The therapy was randomly prescribed, being either cimetidine, 400 mg orally followed by 200 mg every 2 h (group C) or magnesium trisilicate mixture BP, 20 ml every 2 h, plus 30 ml immediately before operation if general anaesthesia was necessary (group M) The paediatricians involved in the care of the babies were unaware of the antacid received by the mother.

At birth, the method of delivery, method of resuscitation and Apgar scores were recorded. A nasogastric tube was passed and the gastric

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contents of the babies tested for acidity and cultured for organisms at intervals over the first 24 h. A wide range of biochemical and haematological variables were studied; these were timed to follow the normal routine of the special care baby unit and included measurements of acid–base status, blood glucose, calcium, sodium, potassium, magnesium, bilirubin and haemoglobin levels, packed cell volume and white cell count. Abnormalities of biochemistry were defined according to Halliday *et al.* (1981).

The progress of the infants was followed until discharge or death and the severity and duration of any complications was noted.

Verbal consent was obtained from the women included in the study, and permission for the trial was granted by the local ethical committee.

Statistical evaluation of results employed Student's *t*-test, χ^2 test, Fisher's exact probability test and Mann–Whitney *U* test where appropriate.

Results

The study took place over 13 months and involved a total of 68 babies (36 in group C and 32 in group M), including several sets of twins. Data in some cases were incomplete—either recordings were not made or the infant left the special care nursery unit before the age at which investigations were scheduled. The women in the two groups matched well for average age, weight, height and parity (Table 1). About half the women were primigravidae. Fewer women in group C had presented early at the antenatal clinic but the mean number of hospital visits was similar in both groups. Similar numbers had suffered from antepartum haemorrhage and premature rupture of membranes (Table 1)

In each group the women received, on average, two doses of antacid (i e 40 ml of magnesium trisilicate mixture or 600 mg cimetidine) Thirteen of the women in group C received narcotic analgesis during labour, while five received diazepam and seven hydralazine; the corresponding numbers in group M were 11, 4 and 5.

The risk category to which the women belonged is shown in Table 2, and there were no differences between the two groups. More women in group M had degrees of pre-eclampsia ($n = 15$) ($P = 0{\cdot}016$) although more women had severe pre-eclampsia in group C (6 compared with 2). Ten women in group C had epidural analgesia compared with only two in group M ($P = 0{\cdot}02$; χ^2 test).

Table 1. Some maternal characteristics

	Group C (cimetidine) (n = 36)	Group M (magnesium trisilicate) (n = 32)
Mean age (years)	27 (5)	26 (5)
Mean weight (kg)	70 (14)	67 (15)
Mean height (cm)	160 (6)	158 (3)
Primigravidae	14	15
Mean no. antenatal visits		
Booking	5 (3·6)	5 (2·5)
Unbooked	3	0
Booked <16 weeks	18*	24
Booked >16 weeks	15	6
Antepartum haemorrhage	7	7
Premature rupture of membranes	9	7

SD is shown in parentheses
*Significant differences between groups $P = 0{\cdot}03$ (χ^2 test)

Table 2. Risk category to which patients belonged

Risk category	Group C (cimetidine)	Group M (magnesium trisilicate)
Gestation <36 weeks	27	20
Birthweight <2000 g	2	2
Other (severe pre-eclampsia, diabetes etc)	7	10

There was no difference in the frequency of spontaneous or induced labour, or in the method of delivery between the groups (Table 3). Nine women in group C received a general anaesthetic for delivery (generally caesarean section) compared with 11 in group M. During labour, abnormalities of fetal heart rate (bradycardia or tachycardia) were recorded in similar numbers of infants in groups C (5) and M (7).

There was no significant difference in the frequency of resuscitative measures required at birth by the two groups (Table 4) and Apgar scores at 1 and 5 min (Table 5) did not differ. Twenty-three infants in group C were male compared with 15 in group M, while four sets of twins were born in group C and three in group M (these differences are not statistically significant).

Mean gestational age, birth length and weight, and weight at 7 and 21 days (Table 6) did not differ significantly. On the average group C

Table 3. Onset of labour and method of delivery

Mode of delivery	Group C (cimetidine)	Group M (magnesium trisilicate)
Onset of labour		
Spontaneous	25	18
ARM and syntocinon	2	2
PGE_2 pessary	1	0
Delivery		
Normal	18	13
Outlet forceps	4	1
Rotation forceps	1	0
Vacuum	1	0
Assisted breech	2	3
Breech extraction	0	3
Caesarean section		
Elective	5	6
Emergency	5	6

ARM, Artificial rupture membranes; PGE_2, prostaglandin E_2

Table 4. Resuscitative measures required

Resuscitation	Group C (cimetidine)	Group M (magnesium trisilicate)
O_2 by face mask	12	12
O_2 by bag with or without naloxone	23	15
Tracheal intubation	1	5

Table 5. Apgar scores in the two groups

	Group C (cimetidine)		Group M (magnesium trisilicate)	
Apgar score	1 min	5 min	1 min	5 min
5	6	1	12	3
6–7	24	3	18	5
8–10	6	32	2	24
Mean (SD)	6 (1·4)	8 (1·5)	6 (1·6)	8 (1·5)

Table 6. Some measurements made in infants

Measurement	Group C (cimetidine)	Group M (magnesium trisilicate)
Gestation (weeks)	34·3 (2·0)	34·5 (2·0)
Birth length (cm)	47·0 (3·6)	45·0 (4·3)
Weight (g)		
Birth	2097 (425)	2103 (513)
Day 7	2079 (352)	2060 (464)
Day 21	2293 (394)	2245 (481)
OFC (cm)		
Birth	31·7 (1·6)	31·4 (2·0)
Day 7	31·8 (1·1)	32.3 (4·2)
Day 21	32·5 (1·1)	32·8 (1·5)

OFC, Occipitofrontal circumference
Results are means (SD)

and group M babies regained their birthweight in 9 and 11 days respectively, the difference was not statistically significant. Mean body temperature on admission to the neonatal nursery unit was 36°C in both groups. No statistically significant difference in haematological or biochemical variables could be demonstrated between the two groups (Table 7). Blood glucose levels showed a similar decline after birth in both groups. Of those infants who developed jaundice, 18 in group C and 20 in group M required phototherapy. The mean highest bilirubin level occurred on day 5 in group C and on day 4 in group M Infants in group M required oxygen therapy for a significantly longer period (median 2 days, range 0–186) than infants in group C (median 1 day, range 0–26) ($P = 0{\cdot}02$, Mann–Whitney U test), but of those who required mechanical ventilation (6 in group C and 5 in group M) duration of ventilation was similar.

Gastric acidity gradually increased over the first 24 h in both groups (Table 8), no differences being observed at any of the times studied. The majority of gastric cultures were sterile in both groups at birth and at 24 h (Table 9). In six instances the organisms cultured were coliforms and in one case (group M) streptococci.

The duration of time spent in the special care nursery unit was similar in groups C and M (26 and 28 days respectively). During this time a large number of complications were documented and these are listed in Table 10. Twenty-five infants in group C and 16 in group M had uncomplicated courses until discharge.

There were two deaths in the infants studied: one in group C died on the second day from respiratory distress syndrome—this baby, of 29 weeks gestation, had severe congenital abnormalities including a tracheo-oesophageal fistula and anal atresia. Another baby, of 31 weeks gestation (group M) had an extremely stormy

Table 7. Results of haematological and biochemical measurements

	Group C (cimetidine)	Group M (magnesium trisilicate)
Mean haemoglobin (g/dl)		
Day 1	18·2 (3·0)	17·5 (2·1)
Day 4	17·8 (2·1)	17·0 (2·5)
Mean PCV (%)		
Day 1	54·1 (8·7)	51·1 (7·1)
Day 4	51·6 (6·1)	49·0 (6·7)
WCC (10^3/µl)		
Day 1	13·6 (6·7)	11·5 (3·8)
Day 4	11·8 (7·9)	7·0 (3·0)
Acid–base balance (1st 24 h)		
Not done	21	13
Normal	4	5
Metabolic acidosis	4	5
Metabolic/resp acidosis	7	7
Mean pH initial Astrup	7·3 (0·1)	7·2 (0·1)
Mean blood glucose (mmol/l)		
Maternal–delivery	6·7 (2·8)	8·2 (4·5)
Cord–delivery	4·8 (2·9)	5·3 (4·1)
Infant 1 h	3·1 (1·5)	2·9 (1·4)
Infant 4 h	3·6 (1·2)	3·6 (1·5)
Mean % cord/maternal glucose	67·2	58·7
Mean highest bilirubin (µmol/l)	194 (39)	193 (39)
Hypocalcaemia	2	6
Hyponatraemia	2	4
Hypomagnesaemia	1	1
Hyperkalaemia	1	5
Hypokalaemia	2	1

SD is shown in parenthesis

Table 8. Gastric pH of infants in two groups

	Group C (cimetidine)		Group M (magnesium trisilicate)	
Time of sampling	*n*	pH	*n*	pH
Birth	16	6·9 (1·1)	16	7·1 (1·3)
1 h	24	5·4 (1·7)	23	5·3 (2·0)
4 h	27	4·1 (1·4)	24	4·2 (1·7)
8 h	31	3·4 (1·3)	23	3·7 (1·7)
24 h	30	3·1 (1·1)	26	3·7 (1·6)

Results are means (SD).

course, requiring mechanical ventilation via a tracheostomy for a very prolonged period, and ligation of a patent ductus arteriosus and eventually died of bronchopulmonary dysplasia at the age of 18 months.

Table 9. Results of culture of infant gastric aspirates

	Group C (cimetidine)		Group M (magnesium trisilicate)	
Results of culture	Birth	24 h	Birth	24 h
Sterile	24	22	25	17
Polymorphs	6	8	6	7
Organisms (on Gram stain)	1	0	0	3
Positive culture	1	2	1	4

Discussion

Mendelson's syndrome continues to be a major hazard facing the parturient requiring general anaesthesia; nine patients, at least four of whom had received routine therapy with magnesium trisilicate mixture, died from this cause in England and Wales in the years 1976–1978 (DHSS 1982) Because of this continuing mortality, research has been directed at establishing alternative safer antacid regimens for labour and H_2-receptor antagonists may have a place in treatment. While Johnston *et al* (1983) found that strict adherence to a 2-hourly regimen of cimetidine administration in labour resulted in gastric pH values >2·5 in approximately 96% of women, to further decrease the number 'at risk' a saline antacid (single dose) can be administered 5 min before general anaesthesia. With this regimen of cimetidine administration, maternal blood concentrations tend to plateau at approximately 1 µg/ml after three doses, corresponding umbilical cord levels being about half the maternal concentration (Johnston *et al.* 1983). This maternal concentration will inhibit maximally stimulated acid secretion by approximately 80% (Pounder *et al.* 1977). Since substantial amounts of cimetidine are present in the fetus and newborn, it is important to monitor any possible effects on infants before the drug can be recommended for routine use.

Neither Johnston *et al.* (1983) nor Hodgkinson *et al.* (1983) had found any adverse effects of maternal cimetidine treatment on babies, although the latter had also subjected them to neurobehavioural examination, which is thought to be a sensitive indicator of drug effects

Table 10. Complications arising in infants in the two groups

Condition	Group C (cimetidine)	Group M (magnesium trisilicate)
Apnoeic attacks responding to		
Stimulation/CPAP	4/0	3/1
Theophylline/IPPV	1/3	1/1
RDS		
Mild	4	4
Moderate	2	1
Severe	6	5
Transient tachypnoea of newborn	4	7
Meconium aspiration syndrome	0	1
Pneumothorax	1	4
Pulmonary haemorrhage	0	1
Persistent pulmonary hypertension	0	3
Septicaemia (with positive culture)	2 (2)	5 (4)
Intraventricular haemorrhage	1	0
Cerebral signs	2	5
Floppy baby syndrome	0	1
NEC		
Abdominal distension/ bloody stools	1	1
Intramural air	0	2
Physiological jaundice	29	28
Treatment for PDA		
None/fluid restriction	3/1	0/1
Ligation or indomethacin	3	2
Bronchopulmonary dysplasia	0	1
Cardiac problems in 1st hour		
Tachycardia	0	1
Failure	1	2

RDS, respiratory distress syndrome; NEC, necrotising enterocolitis, PDA, patent ductus arteriosus, CPAP, continuous positive airway pressure, IPPV, intermittent positive pressure ventilation.

on the central nervous system. However, with high-risk infants, blockade of H_2-receptors could have theoretical disadvantages. Cardiovascular responses to hypoxia, and reduction of gastric acidity, leading to colonization of the gastrointestinal tract, could occur. The present study has shown that gastric acidity develops equally rapidly in 'cimetidine treated' infants as in those exposed to conventional treatment and that no increase in bacterial colonization occurs. This may be due to the short duration of action of cimetidine, or the relative unimportance of histamine in stimulating gastric acid secretion in the newborn. Although total numbers of infants studied were too small for conclusive statements with regard to the serious complication of necrotizing enterocolitis, the worst cases of this syndrome actually occurred in the group treated with magnesium trisilicate.

The most common problem with both groups of infants was, predictably, physiological jaundice, and the infants in which this occurred are numerous enough to conclude that there was no tendency to increased incidence or severity of jaundice in the cimetidine group. Feely *et al.* (1981) found that cimetidine reduced liver blood flow in male volunteers. Lilly *et al.* (1978), giving cimetidine (20–30 mg/kg/day) to children for peptic ulcer found evidence of associated transient cholestasis but no apparent liver cell necrosis. One case of otherwise inexplicable jaundice has been reported in an infant whose mother received cimetidine for peptic ulcer for 1 month before delivery (Glade *et al.* 1980) and the authors suggest a causal relation. However, Chhattriwalla *et al.* (1980) using cimetidine (10–20 mg/kg/day) to effectively treat gastrointestinal bleeding in ill, premature newborn found no hepatic, renal, haematological or neurological effects. While it is possible, therefore, that larger doses of cimetidine may have some effect on hepatic function, it is highly unlikely, as has been demonstrated in this study, that the amounts transferred to the fetus during labour will have any adverse effect.

Jeffreys & Vale (1978) reported raised blood glucose levels after repeated administration of cimetidine but no such effect was observed in the present study as maternal blood glucose levels at delivery were similar in both groups and infant levels declined after birth to a similar extent in the two groups.

Other biochemical and haematological variables studied revealed only a few infants with any abnormalities in both groups. Numbers developing other complications were also small, but no tendency towards any particular problem was demonstrated.

In summary, cimetidine, in the dosage used in labour, has no apparent effect on the gastric acidity, bacterial colonization or development of jaundice in the high-risk infant. Blood glucose levels seem unaffected. Only a small number of babies presented with the necessary requirements for inclusion in this study over a period of 13 months, in a hospital with approximately 2500 deliveries per annum. It was impracticable to prolong this very time-consuming study. Consequently, the numbers studied here are too small other than to state that we found no tendency towards any of the large number of complications investigated, but very large numbers of infants would need to be studied to be more certain. Finally, in view of the very few side-effects recorded, using the more recently available H_2-receptor antagonist, ranitidine, and because of its longer duration of action, it might be a suitable drug for use in labour.

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Iatrogenic neonatal and maternal hyponatraemia following oxytocin and aqueous glucose infusion during labour

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Summary. Maternal and umbilical cord serum sodium and osmolality were studied prospectively in 140 deliveries to investigate whether transplacental hyponatraemia, seen following oxytocin infusion during labour, was due to the antidiuretic effect of oxytocin or was secondary to the infusion of aqueous glucose used as a vehicle for oxytocin, or both. Forty-five women received oxytocin in aqueous glucose for induction or augmentation of labour (oxytocin group), 43 received aqueous glucose infusion alone (glucose group) and 52 did not receive any intravenous infusions (control group). Mean cord sodium levels were significantly lower in the oxytocin (131·4, SD 3·6 mmol/l) and glucose groups (132·5, SD 3·2 mmol/l) than in the control group (135·0, SD 3·0 mmol/l). Hyponatraemia (Na <130 mmol) was seen in 47% and 30% of the infants in the oxytocin and glucose groups respectively, in contrast to only 5·8% of the infants in the control group. Significant negative linear correlations were seen between serum sodium and the dose of oxytocin ($P<0·01$) and log of the volume of glucose solution infused ($P<0·001$). The hyponatraemic newborn infants had a significantly higher incidence of transient neonatal tachypnea (7/37, 19%) than the normonatraemic infants (2%). Our results strongly suggest that infusion of oxytocin and glucose both cause maternal and transplacental hyponatraemia, even in recommended doses. This should be taken in account while planning a safe dose of oxytocin and glucose for infusion during labour.

Neonatal and maternal hyponatraemia have been described following oxytocin infusion during labour (Alstatt 1965; Schwartz & Jones 1978; Dahlenburg *et al.* 1980; Burt *et al.* 1960; Tarnow-Mordi *et al* 1981). Whether this hyponatraemia is caused by infusion of aqueous glucose used as a vehicle for oxytocin, or is due to the antidiuretic effect of oxytocin, or both, is not clear. It had been pointed out that in virtually all the reports of oxytocin-induced hyponatraemia, the women had received >3·5 litres of fluid during labour, usually as 5% aqueous glucose (Feeny 1982) and it was suggested that the infusion of aqueous glucose was responsible for the hyponatraemia, the use of oxytocin during labour does not have any effect on serum sodium levels (Tarnow-Mordi *et al.* 1981; Dahlenburg *et al.* 1980). On the other hand, oxytocin has been shown to have an antidiuretic effect in pregnant women when infused at doses as low as 2–5 mU/min for 10–15 min (Abdul-

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Karim & Rizk 1970). We therefore undertook a prospective study to find out the relative contribution of oxytocin itself, and aqueous glucose, to fetal and maternal hyponatraemia and its effect on the newborn.

Subjects and methods

Three groups of women who had a vaginal delivery in the labour ward of the University Hospital of the West Indies over a period of 6 weeks from 1 March 1982, were studied together with their infants. Group I consisted of women who received an intravenous infusion of aqueous glucose during labour for dehydration (glucose group) and group II comprised women who received oxytocin infusion in aqueous glucose during labour (oxytocin group) (about 90% of the fluids used in groups I and II contained 5 g/dl of glucose and 10% contained 10 g/dl). The women in group III, the control group, did not receive any intravenous fluid therapy or oxytoxin.

An attempt was made to include all consecutive deliveries until there were about 40–50 subjects in each group. Informed consent was obtained from all the women and the study was approved by the ethics committee of the hospital.

Details of pregnancy, labour, type and volume of intravenous fluid therapy, dose and rate of oxytoxin infusion during labour, Apgar score and birthweight of the infant were recorded for all the women by attending medical students or midwives. In all patients the need for oxytocin and/or fluid therapy was determined by the attending obstetrician, using uniform guidelines observed by our labour room medical staff. Oxytocin therapy infusion (5 U/l) was started at a rate of 2·5 mU/min and increments of 2·5–5 mU were made every 30 min until effective uterine contractions were established. At this stage infusion was maintained at the same dose till delivery.

Maternal venous blood was obtained from the anticubital vein on the side opposite to the running infusion, as soon as possible but within 15 min after delivery and cord vein blood was collected in plain glass tubes. Serum was separated by centrifugation and stored at 4°C. Serum osmolality was determined within the next 12 h with an advanced model-2 osmometer, and the rest of the serum was stored at −20°C for serum sodium estimation in batches by flame photometry (Technicon SMA6/60 Autoanalyser)

Statistical significance of the observations was determined by two-tailed *t*-test, and χ^2 test. Correlation between various perinatal factors and maternal and cord serum sodium were determined by the method of least squares. These tests were done with the help of Statistical Programme for the Social Sciences (SPSS).

Results

There were no significant differences between the three groups with respect to maternal age, gravidity, parity, frequency of pre-eclampsia, duration of labour, type of delivery, Apgar score, gestational age and infant birthweight (Table 1). Mean maternal and cord serum sodium levels were significantly lower in the oxytocin and glucose groups than in the control group ($P<0{\cdot}05$) (Table 2).

Distribution of maternal and cord serum sodium levels is shown in Fig. 1. Hyponatraemia (serum sodium ≤130 mmol/l) was observed in 7·7, 22·2 and 33·3% of the women and in 5·8, 30·2 and 46·7% of the infants in the control, glucose and oxytocin groups respectively ($P<0{\cdot}001$, χ^2 test). Severe neonatal hyponatraemia (serum sodium <125 mmol/l) was seen only in the oxytocin group.

Moderate correlation was seen between maternal and cord serum sodium levels at the time of delivery with no systematic difference between paired values (Fig 2). Coefficients of correlation between maternal and neonatal sodium values were 0·73, 0·73 and 0·76 for control, glucose and oxytocin groups respectively.

A low but statistically significant negative correlation was observed between maternal and cord serum sodium levels and total volume of glucose solution infused during labour, as well as between sodium levels and dose of oxytocin infusion (Fig. 3). Gestational age, birthweight, duration of labour and presence of pre-eclampsia were not significantly related to serum sodium levels.

To further define the individual roles of oxytocin and glucose solution in the lowering of serum sodium levels, we compared the serum sodium values between those women in the glucose and oxytocin groups who had received similar volumes of glucose solution during labour. It may be seen from Fig. 4 that the scatter of serum sodium values is apparently similar in the two groups for the women who had received about 500 ml of glucose solution, but in the women who received higher volumes of glucose

Table 1. Clinical characteristics of the three study groups

Characteristics	Control group (*n* = 52)	Group I (glucose infusion) (*n* = 43)	Group II (glucose+ oxytocin) (*n* = 45)
Maternal age (years)	23·3 (4·8)	24·4 (6·8)	23·1 (7·2)
Gestation (weeks)	39·2 (1·3)	39·0 (1·8)	39·6 (1·0)
Duration of labour			
First stage (h)	7·0 (3·3)	10·0 (6·2)	9·7 (5·2)
Second stage (min)	20·1 (13·2)	25·4 (15·2)	29·9 (17·4)
Number with pre-eclampsia	3 (5·9%)	4 (9·8%)	7 (14·6%)
Number with forceps delivery	1 (3·8%)	2 (4·9%)	2 (4·1%)
Apgar score <6	4 (7·7%)	2 (5·2%)	4 (8·4%)
Birthweight (g)	3119·8(476·7)	3020·4(578·6)	3199·0(442·2)

Results are shown as means (SD) or *n*(%) as appropriate

Table 2. Maternal and cord serum sodium and osmolality in the three study groups

		Serum sodium (nmol/l)		Serum osmolality (mosmol/kg)	
Group	(*n*)	Maternal	Cord	Maternal	Cord
Control	(52)	135·4 (3·5)	135·0 (3·0)	280·8 (4·1)	279·7 (4·5)
Glucose infusion	(43)	133·3 (3·3)*	132·6 (3·2)*	278·5 (4·4)	276·4 (5·2)
Oxytocin+glucose	(45)	132·3 (4·4)*	131·4 (3·6)*	276·3 (6·3)*	276·0 (6·5)*

*Significantly less than controls, $P<0·05$; *t*-test.
Results are means (SD).

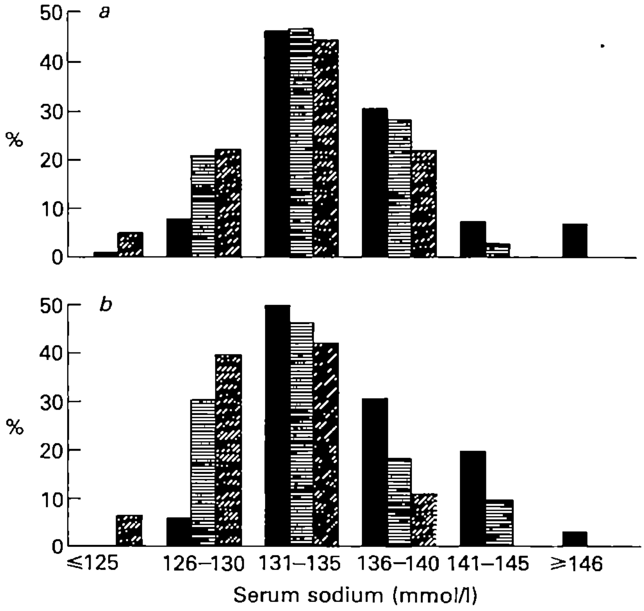

Fig. 1. Distribution of maternal *(a)* and cord *(b)* serum sodium levels in three groups. ▤ Aqueous glucose infusion; ▨ oxytocin in acqueous glucose, ■ controls, no infusion.

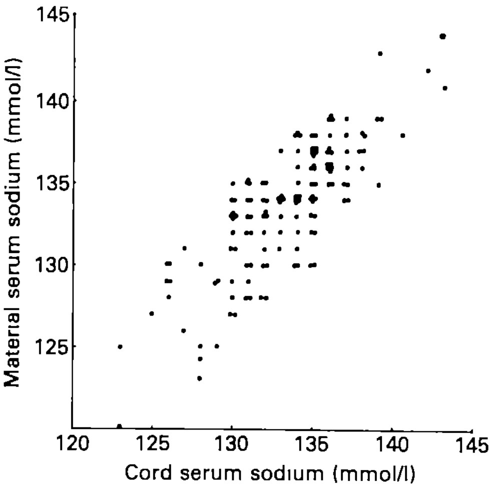

Fig. 2. Correlation between maternal and cord serum sodium levels at the time of delivery (three groups combined)

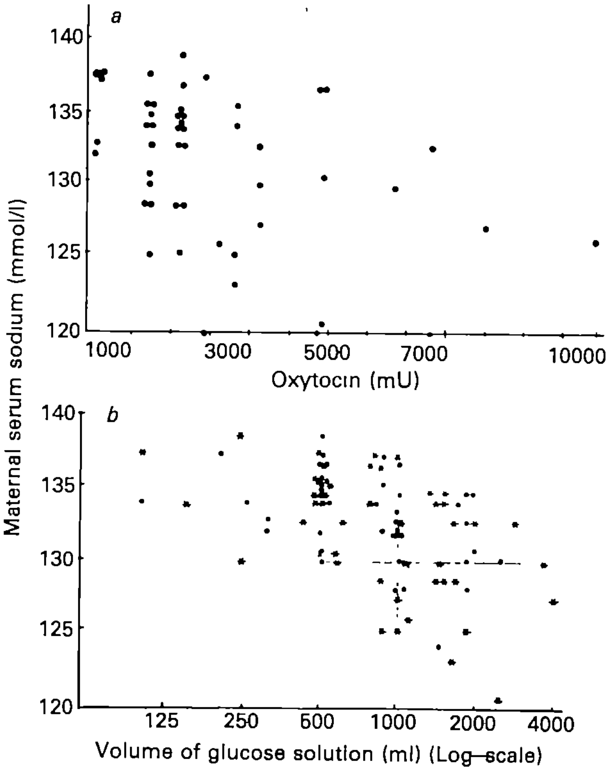

Fig. 3. Correlation between volume of glucose solution infused during labour and maternal serum sodium level at the time of delivery (*b*) ($r = -0{\cdot}47$, $P<0{\cdot}0001$) , and dose of oxytocin and maternal serum sodium level (*a*) ($r= -0{\cdot}34$, $P<0{\cdot}02$)* oxytocin plus glucose solution, ● glucose solution.

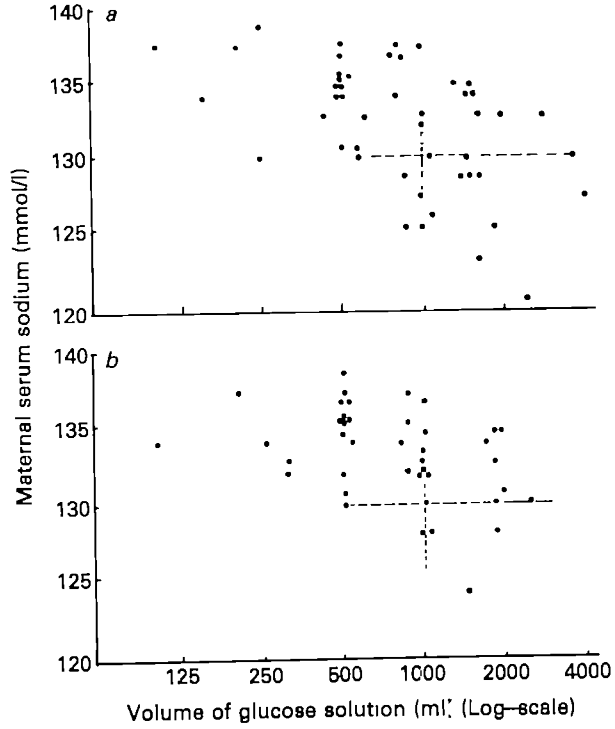

Fig. 4. Scattergram showing relation between volume of glucose solution infused during labour and serum sodium level at the time of delivery in the oxytocin (*a*) ($r = -0{\cdot}52$, $P<0{\cdot}0001$) and glucose only (*b*) ($r = -0{\cdot}42$, $P<0{\cdot}001$) groups. At the volumes of ≥1 litre sodium levels tended to be lower in oxytocin group

solution, serum sodium tended to be lower in those who had also received oxytocin. Indeed, the mean sodium level in women who received ≥1000ml of glucose solution with oxytocin was significantly lower than that in the women who had received similar volumes of glucose solution without oxytocin (Table 3).

Multiple-regression analysis revealed that the volume of glucose solution infused was the only significant factor in lowering maternal and neonatal serum sodium levels in the women receiving <1000 ml of the fluid ($P<0{\cdot}01$ by F-test) and accounted for about 20% of the variation in the sodium levels. In the women who received ≥1000 ml of glucose solution oxytocin was the most important factor negatively influencing maternal and neonatal serum sodium levels, followed by volume of fluid infusion ($P<0{\cdot}001$, by F-test) accounting for about 23·5% variation.

None of the 37 hyponatraemic infants showed neurological manifestations such as excessively poor feeding, apnoea or convulsions. We observed an increased incidence of transient neonatal tachypnea or respiratory distress type II (Avery 1964) in hyponatraemic infants. This was seen in seven of the hyponatraemic infants (19%) compared with only 2% (2/103) of the normonatraemic ($P<0{\cdot}02$). Jaundice (serum bilirubin ≥85 μmol/l) was seen in 54% (20/37) of hypoatraemic compared with only 21% (22/103) of normonatraemic infants ($P<0{\cdot}001$).

Discussion

This study shows that infusion of aqueous glucose and oxytocin during labour is associated with a significant decrease in neonatal and maternal serum sodium and osmolality and a high incidence of dilutional hyponatraemia. Further analysis of the data also shows that in the subjects receiving oxytocin with ≥1000 ml of fluid, oxytocin was the most important factor in reducing maternal and neonatal sodium levels. These findings support a previous suggestion that the use of oxytocin during labour also causes a decrease in maternal and cord serum and osmolality (Singhi & Singh 1979; Spencer *et al.* 1981) which is independent of the infusion of glucose solution and this argues against the con-

Table 3. Maternal and cord serum sodium level and perinatal characteristics in groups I and II subgrouped according to total volume of fluid infused

	Total volume of intravenous fluid			
	<1000 ml		≥1000 ml	
Characteristics	Group I (glucose) (*n* = 28)	Group II (oxytocin+ glucose) (*n* = 25)	Group I (glucose) (*n* = 15)	Group II (glucose+ oxytocin) (*n* = 20)
Serum sodium (mmol/l)				
Maternal	133·9 (0·6)	134·7 (0·7)	132·3 (0·8)	129·7 (0·9)*
Cord blood	132·2 (0·6)	132·6 (0·8)	131·9 (0·6)	130·0 (0·7)*
Maternal age (years)	25·0 (1·15)	23·4 (0·95)	25·6 (1·3)	22·0 (1·0)
Gestation (weeks)	39·1 (0·2)	39 5 (0 2)	39·0 (0·4)	39·7 (0·2)
Length of labour				
First stage (h)	10·6 (1·6)	7·1 (0·9)	8·5 (1·0)	11·7 (1·2)
Second stage (min)	25·2 (3 1)	24·0 (3·4)	25·3 (3·5)	30·1 (3·0)
Pre-eclampsia	2 (8%)	4 (16%)	— 0	3 (15%)
Type of delivery				
Spontaneous	26	24	15	19
Forceps	2	1	0	1
Apgar score <6	0	2	0	1
Birthweight (g)	3071 (79·4)	3256·1 (95·7)	3031·1(115 5)	3113·2 (98 8)
Volume of fluid infused (ml)	490·0 (40·4)	505·4 (46 4)	1370 0(110 0)	1386·2 (69 8)
Rate of glucose infusion (ml/h)	71·6 (10·2)	75·2 (11 5)	186·6 (16·3)	154 3 (18·4)
Dose of oxytocin (mU)	—	2416·7(254·8)	—	2585·0(207·4)
Rate of oxytocin infusion (mU/min)	—	6 7 (1·2)	—	7·4 (1·5)

*P<0·05 by *t*-test.

Results are means (SEM) where appropriate.

clusion drawn by Dahlenburg *et al.* (1980) and Tarrow-Mordi (1981) that oxytocin in the usual doses has no effect on maternal and neonatal serum sodium levels. One of the reasons why these authors could not find any relation between oxytocin and the lowering of serum sodium may be that they did not analyse their results in different fluid groups.

The antidiuretic effect of oxytocin has been noted in pregnant Jamaican women at infusion rates of ≥7 mU/min (Douglas 1965) It was therefore expected that the use of oxytocin during labour in doses used in our study would be accompanied by dilutional hyponatraemia and hyposmolality. What was unexpected was that, with glucose infusion of <1000 ml, oxytocin did not have any significant negative influence on serum sodium levels, even when the mean infusion rate of oxytocin was about 7 mU/min. It is possible that there was not enough water to show an effect with infusions of <1000 ml but an additional reason may be the direct saluretic effect of oxytocin on the kidneys, which has been shown to come into operation only after a certain degree of water retention and expansion of extracellular fluid has been reached (Gupta & Cohen 1972; Leonard & Banks 1980). It has been suggested that oxytocin inhibits sodium resorption in the distal nephron in saline expanded neonatal dogs (Leonard & Banks 1980).

Although the critical range of serum sodium level associated with occurrence of convulsions has been said to be between 120 and 125 mmol/l (Arieff *et al.* 1976), it is interesting to note that none of the infants who had hyponatraemia showed any obvious neurological symptoms during the first few days of life. Similar observations had been made by Tarnow-Mordi *et al.* (1981) and Spencer *et al.* (1981). Recent studies in newborn puppies suggest that even a moderate degree of hyponatraemia caused a significant increase in total extracellular and intracellular brain water within 1 h and a decrease in brain tissue sodium and chloride contents within 3 h, all the changes being in direct proportion to plasma sodium levels (Nattie & Edwards 1981). Raised intracranial pressure caused by brain oedema may be dangerous, but in the newborn infant open sutures and fontanelle probably act as protective devices. But the apparent asymptomatic nature of hyponatraemia should not allay our concern about its occurrence in the infants. In the presence of another factor causing brain oedema such as hypoxia, hyponatraemia may worsen the cerebral oedema. An association between hyponatraemia and neonatal jaundice has also been suggested (Singhi *et al.* 1982). Decreased erythrocytic membrane functions especially that of sodium-potassium-ATPase has been shown in hyponatraemic infants (Sigstrom 1981).

We have also observed a significant association between the occurrence of neonatal hyponatraemia and transient neonatal tachypnea. Normally soon after birth excessive alveolar and interstitial fluid from the newborn is absorbed and drained by the venous circulation and lymphatics (Humphrey *et al.* 1967). A delay in postnatal resorption of pulmonary fluid has been identified as the most probable cause of transient neonatal tachypnea and plasma osmotic pressure is one of the most important determinants of the fluid absorption. A fall in plasma osmotic pressure because of hyposmolality is thus likely to delay absorption of pulmonary fluid and could be one reason for increased incidence of transient neonatal tachypnea. Also the sodium pump is important in adrenalin induced resorption of pulmonary fluid (Strang 1982). It is possible that function of this pump is impaired in the presence of hyponatraemia, which may further contribute to delay in pulmonary fluid resorption.

Induction of labour has clear indications in obstetric practice and oxytocin–glucose solution infusion will probably continue to be the main method. We are concerned about resultant neonatal hyponatraemia following the use of these agents. It has been recommended that, to prevent hyponatraemia, the volume of aqueous glucose infused in women in labour should not exceed 2–3 litres (Feeny 1982), but hyponatraemia has been observed in our population even when the volume of infusion was ≤2 litres. It therefore appears that the restriction of fluid volume alone may not be adequate. The use of sodium-containing fluid may be a partial answer, but we suggest that in the interest of neonatal wellbeing, mothers receiving intravenous fluid and oxytocin should be carefully reviewed for further administration of fluid and oxytocin at each step, especially after the volume of infusion reaches 1 litre. Maternal serum sodium levels should also be monitored as this reflects fetal levels very well and the volume and type of fluid infused must be regulated by these levels. The use of sodium-containing fluids and infusion of oxytocin at a higher concentration than the usual 5 U/l may also be considered so as to limit the volume of infusion to 1 litre as far as possible.

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Effectiveness of vaginal administration of progesterone

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Summary. Vaginal administration of 200 or 400 mg of progesterone in a wax suppository every 12 h in normal women was effective in rapidly achieving and maintaining serum progesterone concentrations at physiological levels appropriate to the midluteal phase of the ovarian cycle and early pregnancy. Given in the follicular phase for 5 days in five subjects at each of two doses, progesterone reached concentrations in serum after 4 and 12 h of 21–105 nmol/l (mean 46·4 nmol/l SD 17·2, $n = 50$) with 200 mg dosage and 21–101 nmol/l (mean 53·8 nmol/l SD 16·6, $n = 49$) with 400 mg dosage. There was no significant reduction in levels between 4 and 12 h after administration, in contrast to previously reported findings, suggesting that the wax base led to slow release of the hormone. The uptake of progesterone in the midluteal phase was assessed in 10 subjects by comparing successive cycles treated with progesterone or placebo in a randomized double-blind manner. Using only the 400 mg dosage, the mean serum progesterone level was raised by 69%, the untreated level being normal (38·17 SD 10·01 compared with 64·49 SD 23·22 nmol/l, $n = 10$). This was despite an assumed concomitant fall in endogenous hormone production as suggested by a 28% reduction in oestradiol-17β levels. Thus vaginal administration of progesterone in wax appears to be effective and convenient, and preferable to the use of other progestogens in various circumstances in which a fetus may be exposed to the drug.

Synthetic progestogens are often administered in circumstances that could expose a fetus to damaging effects of the drug. Uses include prevention of spontaneous abortion (Shearman & Garret 1963), treatment of luteal deficiency causing infertility (Soules *et al* 1977; Rosenberg *et al.* 1980), and assessment of oestrogen state in the investigation and treatment of amenorrhoea (Hull *et al* 1979, 1982*a*). There is also a growing use associated with in-vitro fertilization, to control the preceding cycle (Templeton *et al.* 1984), to supplement the early luteal phase before embryo transfer (Garcia *et al.* 1984), or to provide entire support as when using a donated egg in women with primary ovarian failure (Lutjen *et al.* 1984).

Risks to the fetus include virilization of a female (Wilkins 1960), cardiovascular defects (Janerich *et al.* 1977), neural-tube defects (Greenberg *et al.* 1977; Janerich & Piper 1974) and the VACTERL syndrome (Nora & Nora 1973). Although a true causal link between progestogens and these abnormalities has not been conclusively proven, it seems preferable to use the natural hormone progesterone instead. Unfortunately, there is a lack of information on regimens that may be therapeutically useful.

Progesterone administered orally reaches only a brief peak in the circulation (Whitehead *et al* 1980). Subdermal slow-release implants have not achieved physiological levels (Croxatto *et al.* 1982), and even if higher dosage were effective this is an inconvenient route. Efficient absorption has been demonstrated from an intramuscular injection of progesterone in oil with a half-life of 12–24 h, and vaginally and rectally with a half-life ranging from 6 to 12 h depending on dose and the suppository base (Nillius & Johanssen 1971; Price *et al.* 1983) These studies all concerned the response to a single dose. We therefore report our findings using a convenient vaginal regimen aimed at maintaining blood levels of progesterone within physiological ranges.

Subjects and methods

With approval from the Bristol and Weston Health Authority Ethics Committee, informed volunteers were recruited from normal women undergoing routine laparoscopic sterilization. They were studied early in their natural menstrual cycle or while using oral contraception, when endogenous progesterone is known to be low ('follicular phase study'). A vaginal suppository containing either 200 or 400 mg progesterone BP in an inert wax base (Cyclogest, L. D. Collins & Co) was inserted every 12 h for 5 days. Suppositories of diffferent dose were the same size. Blood was sampled at the start, and each day just before and 4 h after the morning suppository (the earlier sample being 12 h after the previous evening's suppository). These times were chosen to give peak and trough concentrations as suggested by Nillius & Johansson (1971).

To study the uptake of progesterone in the normal midluteal phase, the levels were compared in two successive cycles in sterilized subjects using the active preparation (400-mg dose only) or placebo in a randomized double-blind manner ('luteal phase study'). A suppository was administered every 12 h from day 17 of each cycle for 8 days Blood was sampled at the start, and trough progesterone concentrations (i.e. just before insertion of suppositories) were measured every second day during the luteal phase. Samples were included for study only when found to have been timed 5–10 days before the following menstrual period, i.e. in the midluteal phase. Thus there were usually three samples per cycle, and the mean of their hormone levels was taken. Oestradiol-17β concentrations were also measured as an index of endogenous luteal hormone production. Serum was separated and frozen at −20°C until assay.

All samples from an individual subject were assayed in the same batch. Progesterone was measured after hexane extraction by radioimmunoassay employing tritiated progesterone as marker, sheep antiserum to progesterone-11, hemisuccinate-bovine serum albumin, and scintillation counting after separation using dextran-coated charcoal. The results were not corrected for losses as experiment had demonstrated 90–91% recovery of hormone. The within- and between-batch coefficients of variation were 5–8% and 12–14% respectively. There was no appreciable cross-reaction with any synthetic progestogens taken by the subjects using oral contraception, as indicated by the low basal progesterone values found. Oestradiol was measured after ether extraction by radioimmunoassay using tritiated oestradiol and WHO rabbit anti-oestradiol antiserum, and charcoal separation. Results were not corrected for losses (recovery 95–98%). The within- and between-assay coefficients of variation were 7·3 and 11·6% respectively. Mean hormone values were compared between groups or within individuals by Student's *t*-test and paired *t*-test respectively.

Results

Follicular phase study

The 10 subjects were aged 23–42 years (mean 32·0 years), and only three used oral contraception; five were treated with 200 mg progesterone dosage per suppository and five with 400 mg. Their serum progesterone concentrations are given in Table 1 and summarized in Fig. 1. All the subjects started with a low progesterone level, as expected, which rose within 4 h, and was mostly maintained until the next dose. There appeared to be a further gradual rise over the 5 days of treatment with 400 mg but not with 200 mg dosage, but this rise was not significant. The overall mean value after the higher dose (53·8 nmol/l SD 16·6, $n = 49$) was significantly greater than after the lower dose (46·4 nmol/l SD 17·2, $n = 50$) ($P<0{\cdot}05$), although the difference was small and the observed ranges in the two groups were similar (21–101 nmol/l and 21–105 nmol/l respectively).

Luteal phase study

The 10 subjects were aged 27–39 years (mean 32·1 years). The mean hormone values for the

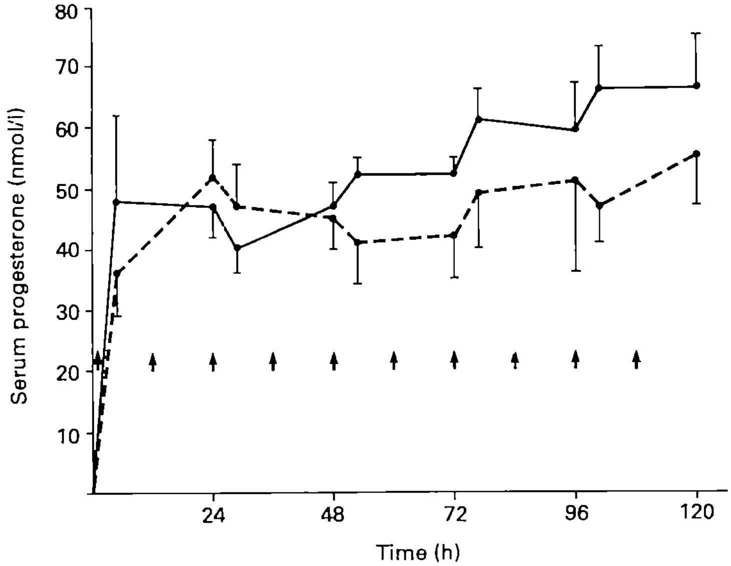

Fig. 1. Mean serum progesterone concentration (± SE) before and 4 h after administration (↑) of 200-mg (●--- ●) or 400-mg (●——●) vaginal progesterone suppositories every 12 h.

midluteal blood samples from each subject, and for the group of subjects, are given in Table 2. Every patient had an increase in progesterone ($P<0{\cdot}001$) and all but two a reduction in oestradiol ($P<0{\cdot}01$) with the effective preparation. The mean progesterone concentration for the group on active treatment was 69% higher than on placebo, and the mean oestradiol concentration was 28% lower.

Discussion

This study demonstrates that a convenient regimen of administering progesterone vaginally in wax-based suppositories (Cyclogest, L. D Collins & Co) can be used in women (a) with low endogenous progesterone levels, to achieve and maintain levels within the normal midluteal range as required for fertility, and (b) in the

Table 1. Serum progesterone concentration (nmol/l) before and after vaginal administration of progesterone at (a) 200 mg and (b) 400 mg dosage

Patient no	Age (years)	Time (h) after each dose										
		0	4	12	4	12	4	12	4	12	4	12
(a) 200 mg dosage												
1	30	<4	30	37	59	29	42	23	42	46	56	46
2	42	<4	63	73	54	39	47	42	31	105	37	84
3	40	<4	24	46	30	50	21	37	45	22	55	42
4*	35	<4	25	59	31	55	64	63	86	58	50	57
5	24	5	37	46	62	50	31	47	41	26	32	44
(b) 400 mg dosage												
6*	37	<4	39	58	52	56	46	63	56	57	65	57
7*	24	5	93	44	45	51	58	48	62	63	56	72
8	33	<4	21	47	31	30	55	48	52	56	55	52
9	32	5	21	34	32	49	49	45	54	36	60	49
10	23	<4	68	46	42	50	—	56	80	84	93	101

*Patients on oral contraception.

luteal phase, to raise progesterone levels into the normal range for early pregnancy.

In our follicular phase study, progesterone administration of 200 mg per suppository resulted in individual circulating progesterone levels of 21–105 nmol/l, and in 400 mg dosage 21–101 nmol/l Although these ranges are similar, the mean was higher with the higher dose (53·8 compared with 46·4 nmol/l) and variability less. Also, taking 28 nmol/l as the lower normal limit, as found in conception cycles using the same assay (Hull *et al.* 1982*b*), only 4% of individual levels in our study with the higher dose compared with 12% with the lower dose fell below that level. In our luteal phase study, the midluteal progesterone levels were normal with placebo (mean 38·2 nmol/l) and raised by 69% with treatment (mean 64·5 nmol/l), which is similar to the normal early pregnancy rise (Lenton *et al.* 1982). The mean increment (26·3 nmol/l) was much less than in the follicular phase. The discrepancy could not be entirely accounted for by suppression of endogenous progesterone production as suggested by the 28% reduction in oestradiol levels. There may have been interference with progesterone absorption from the vagina by the high endogenous levels which might account for relatively small increment with the higher compared with the lower dose in the follicular phase study.

An unexpected finding from the luteal phase study was the suppression of luteal oestradiol production and therefore presumably of progesterone production by treatment with progesterone, although endogenous progesterone is known to be suppressed by synthetic progestogens (Johansson 1971). The latter are thought to inhibit enzyme systems in the corpus luteum, rather than cause luteolysis, because injections of hCG could still increase progesterone levels. How natural progesterone could interfere with luteal function is unclear.

Progesterone levels were maintained for 12 h after administration, compared with the levels at 4 h when the peak was expected (from findings by Nillius & Johansson 1971). This was surprising as the effective half-life found by those authors in response to a single vaginal dose of 100 mg contained in cocoa fat was about 6–8 h. Price *et al.* (1983) recently found more efficient absorption with a polyethylene glycol base, using a 25-mg dose of progesterone, but with a similar effective half-life. Although the difference between those studies and ours may be partly due to differences in dose, it seems more likely that the suppository base we used leads to slow release of the hormone. It is obviously also well retained despite rapid liquefaction of the wax. The preparation may therefore prove effective if administered only once daily, but this remains to be shown. Meanwhile, however, twice daily administration is convenient enough, and the women studied found the preparation was clean and very acceptable.

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Table 2. Mean progesterone and oestradiol concentrations during the midluteal phase in individual subjects with progesterone treatment or placebo

Patient no.	Age (years)	Progesterone concentration (nmol/l)		Oestradiol concentration (pmol/l)	
		Active	Placebo	Active	Placebo
11	27	39·7	24·3	393·0	643·0
12	39	77·0	47·0	460·0	993·0
13	32	106·3	44·0	83·3	363·3
14	33	49·3	40·3	696·7	760·0
15	30	68·0	45·4	343·0	625·0
16	33	52·0	38·0	345·0	506·7
17	34	53·7	22·0	700·0	625·0
18	36	47·7	32·5	353·3	680·0
19	27	101·0	53·5	640·0	570·0
20	29	50·3	34·7	506·7	523·3
Overall mean		64·5	38·2	452·1	629·0
SD		23·2	10·0	192·1	167·6

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Successful treatment of infertile women with oligomenorrhoea using a combination of an LHRH agonist and exogenous gonadotrophins

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Summary. Eight oligomenorrhoeic patients with increased luteinizing hormone (LH) and androgen levels who had failed to conceive during prolonged anti-oestrogen therapy received a new treatment. Large doses of an LH-releasing hormone (LHRH) analogue (HOE 766) were used to suppress circulating gonadotrophin concentrations and block the positive feedback gonadotrophin surge. Ovulation was induced during continued LHRH analogue treatment with exogenous gonadotrophins without interference from the patient's own pituitary. Seven of eight patients conceived rapidly without premature luteinization and without excessive ovarian enlargement. These complications had occurred in control treatment cycles using exogenous gonadotrophins in the absence of the LHRH analogue.

The conventional treatment for infertile women with oligomenorrhoea associated with increased luteinizing hormone (LH) levels (polycystic ovarian syndrome) involves stimulation of follicular growth with clomiphene citrate after which ovulation may or may not require the use of human chorionic gonadotrophin (hCG). However, some patients remain infertile after a year or more of such treatment even though they may show progesterone levels suggestive of ovulation. These patients respond relatively poorly to ovulation induction with exogenous gonadotrophins (Lunenfeld & Insler 1978; Dor *et al.* 1980), with fewer pregnancies than in hypogonadal patients and a high frequency of ovarian enlargement. The results described here are from a study using a new approach to the treatment of these patients. Large doses of an LH-releasing hormone (LHRH) analogue were used to suppress the high LH levels and to prevent the positive feedback surge of LH. Ovulation was then induced using exogenous gonadotrophins.

Subjects and methods

Eight infertile patients aged between 24 and 34 years were studied. All had oligomenorrhoea and increased LH and androgen levels (mean of at least 10 investigation samples) and had failed to conceive after more than 12 months of clomiphene citrate therapy in doses up to 1000 mg/cycle. Previous hormone analyses showed that they were oestrogenized and fulfilled the criteria for WHO group 2 (Lunenfeld & Insler 1978). As a control exercise, before the therapy described below, attempts were made to induce ovulation for one or two cycles with exogenous gonadotrophins alone. Full details of the procedures involved were explained to all patients who gave their informed consent. Seven of the patients had partners with normal seminal analyses.

LHRH analogue treatment and ovulation induction

The protocol was adapted from that used for patients with normal menstrual rhythm (Fleming *et al.* 1982*a*) and involved the administration of the LHRH analogue HOE 766 (D-Ser^3-^{t}BU^6-EA^{10}-LHRH, Hoechst UK, 5×100 μg intranasally) five times each day in order to desensitize pharmacologically the patient's pituitary with respect to LH and FSH release. After 2 to 3 weeks of this treatment the patient continued to self-administer the LHRH analogue whilst follicular growth was induced by the daily intramuscular injection of human menopausal gonadotrophins (hMG, Pergonal, Serono UK Ltd). Follicular growth was monitored by estimating plasma oestradiol (E_2), using a rapid (2-h) radioimmunoassay (unpublished method) and the E_2 concentrations were used to time ovarian ultrasound examinations (Fleming *et al.* 1982*a*). The intention was to observe a follicle with a diameter of 20 mm at the same time as an E_2 concentration between 250 and 3500 pg/ml when the ovulatory dose of hCG (Payne & Byrne Ltd, 5000 i.u., i.m.) would be given. When one, two or three mature follicles were observed, hCG was injected (day 0) to induce ovulation. A mature follicle was defined as having a diameter of $\geq$17 mm with circulating E_2 levels consistent with the number and sizes of all follicles observed. Treatment with HOE 766 was usually continued until 6 days after day 0 (day +6). Further hCG (2500 i.u.) was administered for corpus luteum support on days +3 and +6, and in the first few instances on day +9 as well.

Samples

Plasma samples (from 10 ml whole blood) were taken daily for at least 3 days before the start of treatment with HOE 766 and continued to day 0. Further blood samples were taken either daily to day 6 or at 3-day intervals for estimation of plasma progesterone and E_2. Concentrations of E_2, LH, FSH and progesterone were estimated retrospectively using conventional radioimmunoassays (Coutts *et al.* 1981). Conversion factors for steroid hormone concentrations: pg/ml $E_2 \times 3{\cdot}68$ = pmol/l; ng/ml progesterone × 3·18 = nmol/l

Results

Administration of HOE 766 caused an abrupt surge of LH from the elevated pretreatment levels to a maximum after 24–48 h. Thereafter, as treatment continued, LH concentrations declined slowly to late luteal phase normal cycle levels (12 i.u./l) after mean 11·3 (2·0 SD) days of treatment (Fig. 1). They remained at this reduced level until after ovulation induction The FSH values showed a similar surge but a less markedly delayed subsequent decline.

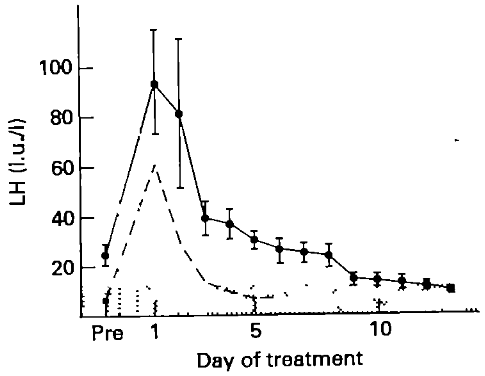

Fig. 1. Effect of LHRH analogue treatment on plasma LH levels •——• Mean (±SEM) concentrations in eight patients with oligomenorrhoea and elevated LH (pre = pretreatment). - - - Mean concentrations in five patients with normal menstrual rhythm and normal LH (treatment initiated during the luteal phase). Stippled area represents levels seen in the normal cycle during the late luteal phase.

In the cycles treated with HOE 766, stimulation of follicular growth with hMG followed a similar pattern to that in hypogonadal patients treated conventionally (Lunenfeld & Insler 1978). Multiple follicular development was observed (by ultrasonography) in all patients and plasma E_2 levels were consistent with the number and size of the follicles observed (Fleming *et al.* 1982*b*). However, in the control (absence of HOE 766) cycles, the E_2 levels often peaked before day 0, around the time of onset of luteinization (Table 1) despite continued hMG treatment. This problem was eliminated in the cycles treated with HOE 766 since peak levels of E_2 occurred always on day 0.

In the control cycles the elevated E_2 levels (250–3500 pg/ml), experienced during follicular

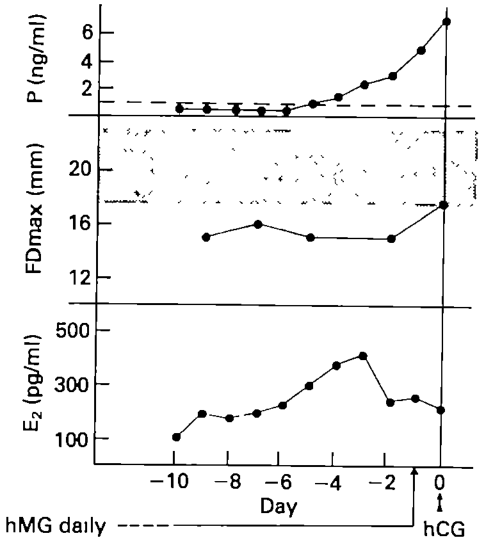

Fig. 2. Progesterone (P), follicular diameter (FD) and oestradiol (E_2) profiles of a patient during induction of ovulation with exogenous gonadotrophins in the absence of LHRH analogue showing premature luteinisation. Results show the period after 3 days of hMG treatment with the rise in E_2 levels starting on day '−10' The progesterone concentrations rose above follicular phase (dashed line) levels from day −4 when the largest follicle (FDmax) was still smaller than the normal pre-ovulatory diameter (stippled area). A follicular diameter of 20 mm was not achieved in this patient despite continued hMG treatment.

growth, induced positive feedback surges of LH superimposed upon the already high levels. Consequent luteinization of the follicles (plasma progesterone >1·5 ng/ml) occurred up to 3 days before the ultrasound identification of a mature follicle and consequently a diameter of 20 mm was not always obtainable. An example of premature luteinization is shown in Fig. 2, where the first progesterone rise occurred on day −4 when the largest follicular diameter was only 15 mm, representing luteinization of an immature follicle. Under these circumstances the normal follicular phase relation between follicular growth and circulating E_2 levels broke down despite continued hMG treatment, as shown in Table 1 where peak E_2 levels were often observed before day 0 in the control cycles. Therefore, direct comparison of E_2 profiles in control and treated cycles was not possible. During the experimental cycles treated with HOE 766 and hMG the endogenous LH surges in response to the elevated E_2 levels were eliminated (Table 1), hCG was administered when a mature follicle (diameter = 20 mm) was observed and E_2 concentrations peaked on day 0 in all patients.

Comparison of the total dosage of hMG used in control cycles and cycles treated with HOE 766 (Table 1) showed no difference between the two groups. Seven of the eight patients conceived during the treated cycles and the five children born so far have all been normal.

Ovarian enlargement

Following hCG administration a proportion of patients suffer from ovarian enlargement and subsequent abdominal discomfort and related morbidity. This is a serious side-effect of ovulation induction using exogenous gonadotrophins (Lunenfeld & Insler 1978). Ovarian enlargement occurred more often in the control cycles than when endogenous gonadotrophin levels were suppressed with HOE 766 (Table 1).

Discussion

Eight patients with high LH levels were treated with the LHRH analogue HOE 766, resulting in normal concentrations (<12 i.u./l) after 9–14 days therapy. The time taken for the high values to be suppressed to normal was longer than that taken in women with normal LH levels before therapy (4–5 days, Fleming *et al.* 1982*a*). Ovulation was induced successfully and conception occurred rapidly in seven patients. The successful application of this new method of treatment in this group of patients shows that with the suppression of LH and the inhibition of positive feedback responses to elevated E_2 concentrations, ovulation can be induced successfully. There were seven pregnancies in 12 cycles in eight patients.

All patients had shown increased progesterone concentrations suggestive of ovulation under previous regimens but had failed to conceive. This was probably due to two factors: inaccurate assessment of ovulation and innaccurately timed coitus. The pharmacological induction of follicular growth causes E_2 production from multiple follicles and supranormal circulating E_2 concentrations. We suggest that patients with 'intact' pituitaries can respond to this with a positive feedback surge of LH which is likely to occur when the largest follicle is immature, since the pituitary is unable to distinguish between E_2 produced by a single or

Table 1. Details of control and treatment cycles

	Control cycle						Cycle treated with HOE 766						
					Peak E_2						Peak E_2		
Patient no.	Cycle	Day of premature luteinization	Ovarian enlargement	No. of hMG ampoules	pg/ml	Day	Cycle	Premature luteinization	Ovarian enlargement	No. of hMG ampoules	pg/ml	Day	Pregnancies
1	1	−2	++	20	650	−1	1	—	–	45	480	0	1
2	1	−2	++	36	1000	0	1	—	–	27	900	0	—
							2	—	–	24	1400	0	twin
3	1	−2	+	26	250	−1	1	—	–	34	280	0	—
							2	—	–	27	470	0	1
4	1	−1	++	16	850	0	1	—	–	20	900	0	—
							2	—	–	18	450	0	1 abort
5	1	−1	–	16	1600	−1	1	—	(+)	17	1800	0	twin
	2	>P—No hCG	+	14	2000	NA							
								—	–				
6	1	−1	–	22	750	−2	1	—	–	20	1250	0	1
	2	−2	–	21	700	−2		—	–				
7	1	−3	–	37	800	−1	1	—	–	34	1800	0	—
							2	—	–	30	1500	0	—
8	1	>P—No hCG	+	12	3500	NA	1	—	–	20	2500	0	—
	2	>P—No hCG	+	13	2000	NA	2	—	–	28	1500	0	1

++ Ovarian enlargement palpable abdominally; required hospitalization.

>P—No hCG, Excessive follicular development with luteinization, hCG not administered

NA, Not applicable.

multiple follicles. Inappropriate luteinization without the ovulation of a viable oocyte would follow these endogenous LH surges. Administration of hCG after this would have no useful effect and coitus would be incorrectly timed. The use of exogenous gonadotrophins for the induction of ovulation in patients with polycystic ovaries has been shown to be less successful in terms of pregnancies per treatment cycle than in hypo-oestrogenic patients (Lunenfeld & Insler 1978), possibly because of 'premature ovulation' as in oestrogenized patients so treated (Gemzell *et al.* 1978). LH surges and premature luteinization did not occur during ovulation induction in any patient treated with HOE 766 to suppress endogenous gonadotrophin activity. This new combined treatment allows accurate timing of ovulation and coitus, as is possible in hypo-oestrogenic patients, and may be equally effective in terms of pregnancies per treatment cycle. It may also lessen the risk of one of the major side-effects of ovulation induction—excessive ovarian enlargement.

Acknowledgment

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Hormonal profiles in the follicular phase, luteal phase and first trimester of pregnancies arising from in-vitro fertilization

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Summary. The hormonal profiles for oestradiol-17β, progesterone, prolactin and β-human chorionic gonadotrophin (β-hCG) are documented for the first 24 pregnancies arising from in-vitro fertilization during a collaborative project between the University of Western Australia and PIVET Laboratory. All patients had ovarian follicle stimulation with clomiphene citrate, sometimes combined with human menopausal gonadotrophin and all had oocyte recovery undertaken 36 h after injection of 5000 i.u. hCG. The follicular phase profile indicated that patients were admitted for the hCG injection when oestradiol-17β levels were around 1500 pmol/l per follicle with a dimension of ≥1·6 cm on ultrasound. Luteal phase data indicated that oestradiol-17β and progesterone levels were two to three times higher than that expected during spontaneous conception cycles and those pregnancies which subsequently aborted had significantly lower levels in the late luteal phase. During pregnancy elevated oestradiol-17β and progesterone levels were maintained through the early weeks during organogenesis while the β-hCG profile was similar to that reported for spontaneous pregnancies arising without ovarian stimulation. Six women aborted and the other 18 pregnancies have generated 22 infants.

The first pregnancies leading to viable offspring by in-vitro fertilization and embryo transfer were achieved without ovarian stimulation (Steptoe & Edwards 1978; Lopata *et al.* 1980; Edwards *et al.* 1980). Greater efficiency and improved pregnancy rates have followed oocyte recovery in stimulated cycles (Trounson *et al.* 1981; Speirs *et al.* 1984) and most current reports concern the use of clomiphene citrate, human menopausal gonadotrophin (hMG) or a combination of both (Speirs *et al.* 1984; Garcia *et al.* 1983, Yovich *et al.* 1984*a,b*). Oocyte recovery is generally undertaken 34 to 36 h after an injection of human chorionic gonadotrophin (hCG) or following a spontaneous LH surge (26–32 h after onset detected in urine and 32–36 h after detection in serum). To date, the luteal phase has remained largely unsupported by any therapy although some reports indicate that hCG, progesterone and progestogens have been used (Feichtinger *et al.* 1982; Yovich *et al.* 1982, 1984*c*) This report covers the hormonal details for the first 24 pregnancies generated in the University of Western Australia/PIVET Laboratory in-vitro fertilization programme and provides a unique opportunity to assess the follicular and luteal phase characteristics for in-vitro fertilization cycles during which pregnancy was achieved. It also allows a comparison of prospective hormonal data for ongoing and aborting pregnancies.

Patients and methods

The first pregnancy from the University of Western Australia/PIVET Laboratory in-vitro fertilization project arose from a small pilot study and led to the birth of a child in July 1982 (Yovich *et al.* 1982). Subsequently a larger programme combining both service and research was developed (Yovich *et al.* 1984*b*) and the additional 23 pregnancies were generated over 12 months between July 1982 and July 1983.

The clinical details of the 24 patients is the subject of a separate report. The majority were included in the in-vitro fertilization programme because of irreparable tubal disease, but some had been included with endometriosis, oligospermia (Yovich & Stanger 1984), heterologous sperm antibodies (Yovich *et al.* 1984*a*), unexplained infertility and one who failed to conceive despite successful suppression of hyperprolactinaemia using bromocriptine. All patients were stimulated from day 2 of the cycle, 15 with clomiphene citrate alone and nine with clomiphene citrate/hMG (C/hMG). Follicle development was monitored by daily ultrasonography, cervical scores and a serum hormonal profile (oestradiol-17β, progesterone and luteinizing hormone [LH]) as previously described (Yovich *et al.* 1984*b*). Each was given hCG about 36 h before oocyte recovery. Generally, those patients who had initiated an LH surge before the hCG injection were not scheduled for ovum aspiration, hence none of the 24 patients who conceived had ova collected following a spontaneous LH surge. The oocyte recovery, embryo culture and embryo transfer techniques have been fully described (Yovich *et al.* 1984*b*).

Sampling and assay methods

Hormonal assays were undertaken on early morning serum samples. The follicular phase was monitored daily for 5–8 days before oocyte recovery which was designated as Day 14 (fixed reference point) with the follicular and luteal days adjusted accordingly. Patients admitted for the hCG trigger injection had a blood sample collected immediately before the injection for LH assay in order to determine retrospectively whether a spontaneous surge was underway. In each case a mid-luteal blood sample was taken on day 21 for serum oestradiol-17β, progesterone, and prolactin and thereafter every third day for oestradiol-17β, progesterone and β-hCG until pregnancy was diagnosed by an elevated β-hCG level of ≥30 i.u./l on or after day 30 and rising on subsequent samples. Day 30 was selected to avoid possible confusion in those cases given hCG luteal support therapy. Thereafter a weekly serum sample was collected and assessed for oestradiol-17β, progesterone and β-hCG until 12 weeks gestation with a final sample at 16 weeks.

Oestradiol-17β and LH were assayed by a non-extraction double-antibody radioimmunoassay (Mallenkrodt, Melbourne, Australia), progesterone by Coat-a-Count solid phase radioimmunoassay (Diagnostic Products, Los Angeles, California) and both quantitative β-hCG and prolactin by double-antibody immunoassay (Amerlex, Amersham, England). The 95% confidence limit of sensitivity for β-hCG is 4 i.u./l.

Luteal support

Some patients conceived during a randomized study of luteal support comparing intramuscular hCG (1000 i.u. on days 18, 21, 24 and 27) and oral medroxyprogesterone acetate (MPA) (40 mg/day from day 15) with no therapy. That study has been reported (Yovich *et al.* 1984*c*) noting no difference in the pregnancy rates for the three groups, but an apparently better outcome for those pregnancies given hCG support. Blood samples for hormone assays were always taken before the hCG injections

Early pregnancy support

Patients who presented with any vaginal bleeding after pregnancy was diagnosed were given oral MPA (80 mg to 120 mg/day) until 16 weeks gestation in an attempt to prevent abortion. In patients whose β-hCG levels continued to fall and ultrasound confirmed a blighted ovum or missed abortion, MPA was stopped and curettage undertaken. Histology on the evacuated uterine contents of the six patients with spontaneous abortion confirmed trophoblastic tissue on each occasion. Three patients developed poor gestational sacs on ultrasound and aborted in the early weeks whilst three developed advanced anembryonic sacs, aborting between 10 and 12 weeks gestation.

All data are recorded with arithmetic means and standard error (SEM) limits. The hormonal data were converted to logarithmic values before being analysed by single analysis of variance (Zar 1974) except for the luteal hormone levels which were compared by Students *t*-test.

Results

By day 13 the 15 patients stimulated with clomiphene citrate alone generated 46 ovarian follicles with dimensions of ≥1·6 cm on ultrasound with an overall mean diameter of 1·89 (SEM 0·06) cm to yield an average of 3·1 follicles per patient. Oocytes were recovered from 41 follicles (89%) with 35 (85%) developing to the stage of cleavage However only 34 embryos were transferred as one contained three pronuclei at 16 h after insemination. Of the nine patients given hMG, 51 large follicles developed, with an average of 5·6 per patient. Forty-one oocytes were recovered (81%) with 34 cleaving embryos generated (83%), all of which were transferred.

Follicular phase

The follicular phase lengths measured from the onset of the cycle (first day of menstrual bleeding) until the day of aspiration was similar in the clomiphene citrate (14·4, SEM 0·32 days) and C/hMG groups (14·4, SEM 0·45). The follicular phase oestradiol-17β levels are shown in Fig. 1 along with changes in the cervical score. The mean oestradiol-17β level per follicle of ≥1·6 cm was 1586 (SEM 154·0) pmol/l in the clomiphene citrate alone group and 1379 (SEM 139·5) pmol/l in the C/hMG group on day 12 when the decision to give the hCG trigger was made. The level of rise of oestradiol-17β was significantly greater for those with added hMG throughout the follicular growth phase up to day 12, ($0·001<P<0·01$). A significant rise in oestradiol-17β levels was also noted between day 12 and the day after hCG (day 13) in the C/hMG group ($0·01<P<0·05$) but not confirmed in the clomiphene citrate group. A concomitant rise in the cervical mucus score (Insler *et al.* 1972) was often used as an additional index for the timing of hCG when the oestradiol-17β levels were rising. Although a slightly higher level was noted on day 12 for the C/hMG group, the cervical scores were similar on the day after, with both groups scoring 9 points out of a possible maximum of 12. A small proportion of patients failed to demonstrate a rise in cervical score despite rising oestradiol-17β levels and enlarging follicles. The LH levels are shown in Fig. 2 along with progesterone which was used as a supplementary index of luteinization. The LH levels were not significantly different between the clomiphene citrate and the C/hMG group. From day 8 to day 12, LH levels appeared to fall but the drop was not statistically significant ($0·05<P<0·10$). From

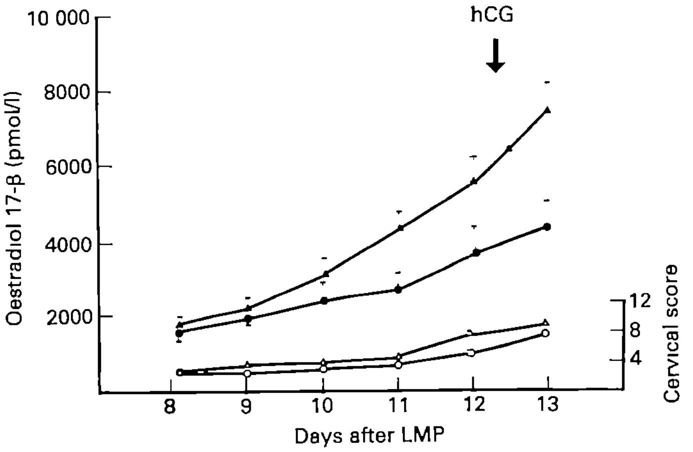

Fig. 1. Change in follicular phase serum oestradiol-17β (solid symbols) concentration and cervical score (open symbols) with time before and after hCG administration (arrow) in clomiphene citrate (● ○) and clomiphene citrate/hMG (▲ △) stimulated in-vitro fertilization conception cycles. LMP, Last menstrual period

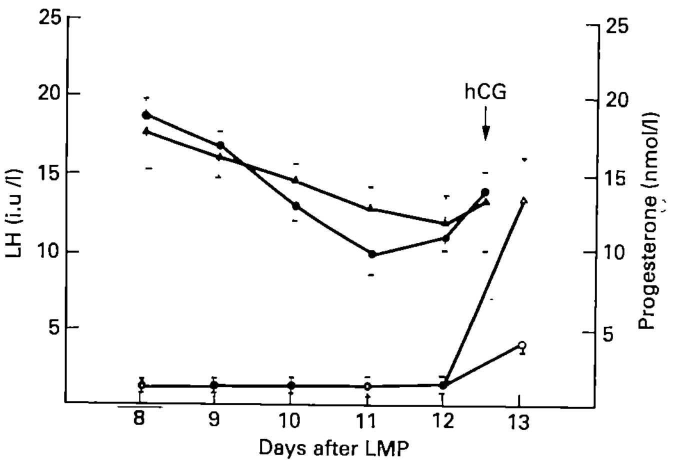

Fig. 2. Change in follicular phase serum LH (solid symbols) and progesterone (open symbols) concentrations with time before and after hCG administration (arrow) in clomiphene citrate (● ○) and clomiphene citrate/hMG (▲ △) stimulated in-vitro fertilization conception cycles. LMP, Last menstrual period.

day 12, LH values were increased slightly in the evening blood sample before the hCG injection although in no case was the value >2SD above the follicular phase mean for the patient and progesterone levels had not risen implying that the patient had not yet started an LH surge. Progesterone levels did not change from day 8 to day 12 but rose significantly after the hCG injection ($P<0{\cdot}001$), the rise being greater in the C/hMG group ($P<0{\cdot}05$).

Luteal phase

Luteal phase oestradiol-17β levels are shown in Fig. 3 with ongoing pregnancies charted according to their follicular phase stimulation regimen,

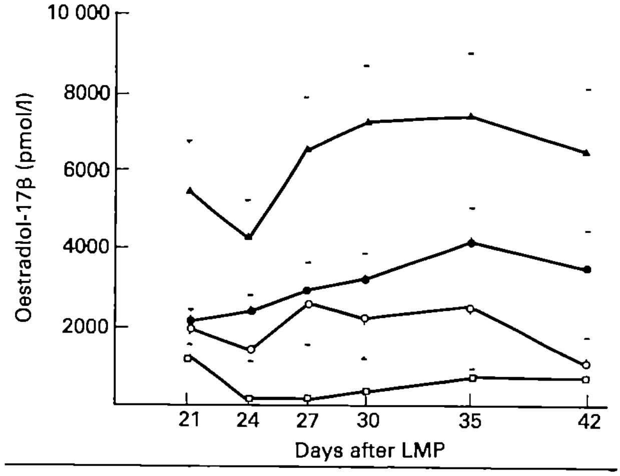

Fig. 3. Serum oestradiol-17β concentration in the mid- and late luteal and early pregnancy phase of successful (solid symbols) and unsuccessful (open symbols) in-vitro fertilization conceptions as a function of the regimen of follicle stimulation (●, clomiphene citrate; ▲, clomiphene citrate/hMG; ○, combined regimen MPA; □, clomiphene citrate/MPA in luteal phase) LMP, Last menstrual period

and the aborting group categorized separately. The luteal phase data demonstrates high oestradiol-17β levels (mean 3329, SEM 555 pmol/l) at the mid-luteal point with persisting elevation throughout the luteal phase and into early pregnancy. It can be seen that the C/hMG group had higher oestradiol-17β levels throughout the luteal phase. Ten patients had hCG support injections and three had been given MPA for luteal support, but no significant difference was noted in oestradiol-17β levels for ongoing pregnancies given luteal support. There was a plateau effect from the luteal phase into the first weeks of pregnancy. Those patients who subsequently aborted did not show significantly reduced oestradiol-17β levels when compared with the ongoing clomiphene citrate group until after day 30 of the cycle, unless they had been given MPA support therapy when oestradiol-17β levels were markedly reduced from day 24 (two observations only). Similar findings were noted for progesterone (Fig. 4) where it can be seen that overall progesterone rose significantly from the beginning to the end of the luteal phase ($0{\cdot}01<P<0{\cdot}05$) when levels also plateaued into early pregnancy. This rise was more pronounced in the C/hMG group ($0{\cdot}001<P<0{\cdot}01$) than the clomiphene citrate only group ($0{\cdot}05<P<0{\cdot}10$). The mean mid-luteal progesterone level was 155 (SEM 92·4) nmol/l on day 21 with persisting elevation into early pregnancy. Again it can be seen that the aborting group had lower progesterone levels with a gradual reduction from day 30. Those having MPA support were also low throughout the luteal phase. These findings predated the abortion process by 2 to 8 weeks although the diagnosis was undoubtedly delayed by the use of MPA in some patients Advanced anembryonic sacs were demonstrated in three patients at between 10 and 13 weeks gestation.

Quantitative β-hCG levels are shown in Fig. 5. Ongoing pregnancies had β-hCG levels of $\geqslant$30 i.u./l by day 27 and no difference was noted in the clomiphene citrate and C/hMG groups. Aborting pregnancies failed to reach diagnostic levels of hCG until day 30 and values were significantly lower than in ongoing pregnancies ($0{\cdot}01<P<0{\cdot}001$). Subsequently, apart from one patient in the C/hMG group with a normal high value on day 35, hCG levels in those destined to abort continued to demonstrate widening disparity from the ongoing group. Patients stimulated with clomiphene citrate and given either MPA or hCG support during the luteal phase showed no difference in β-hCG levels from unsupported cycles. Mid-luteal (day 21) prolactin estimates revealed similar levels for the clomiphene citrate (mean 353, SEM 82·5 nmol/l) and C/hMG groups (292, SEM 81·2 nmol/l) for ongoing pregnancies but the

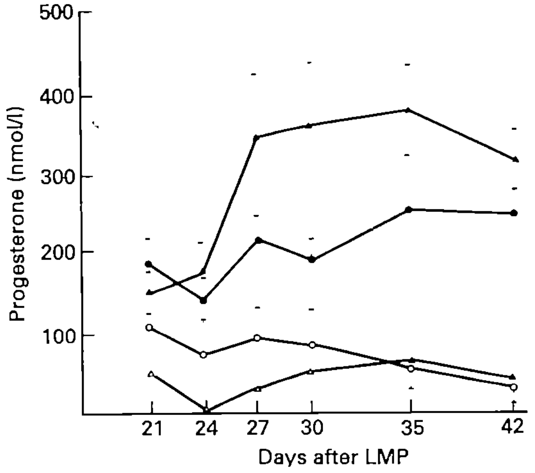

Fig. 4. Serum progesterone concentration in the mid- and late luteal and early pregnancy phase of successful (solid symbols) and unsuccessful (open symbols) in-vitro fertilization conceptions as a function of the regimen of follicle stimulation (●, clomiphene citrate; ▲ clomiphene citrate/hMG; ○, combined regimen MPA; △ clomiphene citrate/MPA in luteal phase). LMP, Last menstrual period

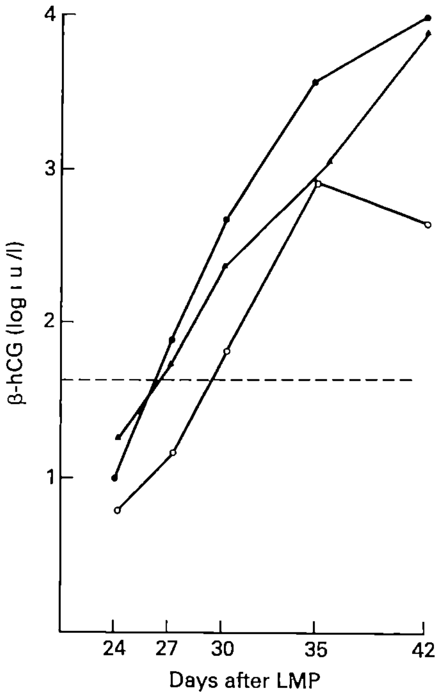

Fig. 5. Serum β-hCG concentrations in the late luteal and early pregnancy phase of unsuccessful (○) conceptions and successful clomiphene citrate (●) and clomiphene citrate/hMG (▲) stimulated in-vitro conceptions. Patients were considered pregnant when the concentration exceeded 30 i.u /l (dotted line)

patients who subsequently aborted (five clomiphene citrate and one C/hMG) tended to have lower values (mean 173, SEM 38·1 nmol/l) ($0{\cdot}05<P<0{\cdot}1$).

Pregnancy

The combined oestradiol-17β, progesterone and quantitative β-hCG information was recorded weekly to 16 weeks gestation for the 18 ongoing pregnancies in this study (Fig. 6 and Table 1). It can be seen that the luteal phase mean levels of progesterone gradually declined by week 7 of pregnancy to 196 (SEM 35) nmol/l with values maintained until week 11. An apparent decline thereafter was not confirmed at the 16 week observation. Oestradiol-17β levels were maintained at luteal values until week 11 when a significant rise was noted in the ensuing observations including week 16 ($0{\cdot}01<P<0{\cdot}05$). Quantitative β-hCG estimations continued rising rapidly with a peak of 70 296 (SEM 14 762) i.u./l centered around weeks 9 to 11, declining to plateau levels at 18 350 (SEM 4 917) i.u./l units from week 12.

From Table 1 relevant hormonal data has been documented with reference to the use of MPA during the luteal phase of the cycle and during the pregnancy. It can be seen that those patients who were given MPA during the luteal phase and continuing into pregnancy (MPA/MPA), demonstrated overall lower oestradiol-17β and progesterone levels throughout the first trimester when compared with those patients who had no support therapy and those who had MPA support after the pregnancy was diagnosed. Occasional low β-hCG levels in the MPA/MPA group are of doubtful significance given the exponential rise of hCG, the small number of observations and the fact that a single

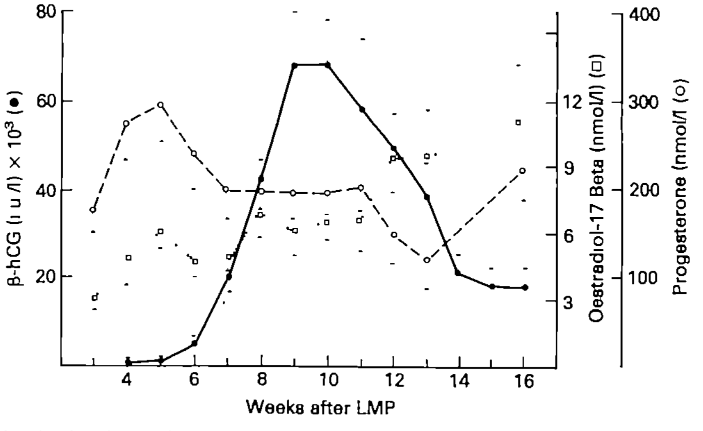

Fig. 6. The change in serum oestradiol-17β (□), progesterone (○) and hCG (●) over the first trimester of successful in-vitro fertilization conceptions arising from clomiphene citrate and clomiphene citrate/hMG stimulated cycles. LMP, Last menstrual period.

Table 1. Partition of weekly serum oestradiol-17β, progesterone and β-hCG concentrations during the first trimester of in-vitro fertilization conceptions as a function of exposure to medroxyprogesterone acetate (MPA) during the luteal phase or pregnancy

			Gestation (weeks from last menstrual period)								
Hormone	MPA[a]	No of patients	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10	Week 11	Week 12	Week 16
Oestradiol-17β (pmol/l)	−/−	6	5047 (954)	4285 (1013)	4873 (583)	8220 (2452)	5974 (1659)	7628 (1581)	7903 (2535)	8530 (2386)	13605 (1852)
	−/+	9	7045 (956)	6173 (988)	6151 (864)	7229 (631)	7328 (1374)	7624 (958)	8085 (2116)	11621 (3707)	17749 (7071)
	+/+	3	2196 (151)	1930 (290)	1922 (241)	2630 (359)	3635 (654)	3447 (847)	2762 (1122)	4810 (487)	11682 (2916)
Progesterone (nmol/l)	−/−	6	311 (68)	178 (50)	112 (31)	132 (32)	166 (49)	135 (21)	123 (22)	118 (33)	189 (20)
	−/+	9	381 (60)	307 (51)	268 (48)	312 (45)	230 (30)	268 (48)	275 (40)	249 (45)	249 (39)
	+/+	3	150 (20)	168 (37)	123 (48)	60 (27)	59 (28)	89 (13)	127 (26)	101 (24)	140 (58)
β-hCG (i u /l)	−/−	6	3205 (942)	10400 (3639)	34400 (8857)	75156 (27430)	68468 (12933)	60633 (7019)	40400 (5397)	36825 (6924)	22000 (6557)
	−/+	9	3535 (1112)	11279 (1717)	29500 (4683)	75121 (18021)	57875 (10937)	58314 (11188)	54571 (966)	47150 (11831)	18485 (5360)
	+/+	3	1364 (690)	4933 (348)	18733 (392)	23000 (5999)	69475 (6024)	58750 (5749)	57233 (8946)	42200 (14029)	22000 (8020)

[a] −/− denotes MPA not given, −/+ denotes MPA given during pregnancy, +/+ denotes MPA given during the luteal phase and pregnancy (see text)
Results are shown as mean (SEM)

Table 2. Luteal and early first trimester serum hormone levels of clomiphene citrate-stimulated ongoing in-vitro fertilization conceptions with or without luteal support

			Days after last menstrual period					
Hormone	Type of support	Number of patients	Day 21	Day 24	Day 27	Day 30	Day 35	Day 42
Oestradiol-17β (pmol/l)	Nil	3	2510 (742)	2802 (920)	3128 (584)	3427 (103·9)	4752 (1373)	3190 (948)
	hCG	4	2383 (450)	2808 (410)	4240 (1370)	4215 (807)	5377 (1045)	5266 (1761)
	MPA	3	1312 (407)	1015 (155)*	1235 (217)*	975 (325)*	2196 (151)*	1930 (290)
	Total	10	2113 (359)	2358 (410)	2917 (709)	3207 (628)	4851 (837)	4653 (843)
Progesterone (nmol/l)	Nil	3	155 (92·4)	134 (32·6)	241 (78·4)	178 (57·3)	334 (106·1)	191 (69·3)
	hCG	4	204 (37·9)	181 (58·5)	228 (38·9)	208 (51·6)	248 (69·5)	322 (133·5)
	MPA	3	210 (61·0)	76 (5·5)*	173 (3·0)	183 (25·0)	150 (20·5)	168 (37·0)
	Total	10	189 (33·0)	142 (29·5)	220 (29·3)	192 (27·4)	255 (70·3)	247 (64·9)

* Denotes a hormone level significantly lower ($P<0·05$) than observed with nil support
Results are mean (SEM)

reading was taken to represent 1 week. From Table 2, it can be seen that the reduced oestradiol-17β levels were apparent from day 21 and reduced progesterone levels from day 24 in those patients given MPA from day 15.

Discussion

In analysing the hormonal data for those patients who conceived after in-vitro fertilization, it was anticipated that an optimal range within the follicular phase could form the basis for selecting patients to proceed to ovum aspiration. Data from the luteal phase might detect those patients who were likely to have conceived and possibly define a sub-group for the consideration of luteal support therapy. An analysis of the early pregnancy hormonal changes is unique in having the fixed reference point of oocyte recovery ('ovulation'), and it was anticipated that the prognosis of each pregnancy might be shown from the data as well as providing an opportunity to analyse the effects of hormonal support therapy, both in the luteal phase and during the early weeks of pregnancy.

The follicular phase data demonstrate that satisfactory follicle development is reflected by steadily rising oestradiol-17β levels with a supportive rise in cervical score within the final 2 days before oocyte recovery. LH levels remained low and demonstrated an apparent decline over the 5 days before hCG injection while progesterone levels, remaining very low up to the time of hCG injection, subsequently demonstrate the rise expected with luteinization of the follicle. The rise was significantly greater with C/hMG, presumably due to the increased number of follicles present in that group.

It is relevant to regard the day of oocyte recovery to be equivalent to that of the day of 'ovulation' as this corresponded with the expected early luteinization effect (rising serum progesterone) and the subsequently successful development of embryos ensuing from oocytes inseminated a few hours after collection signifying that the oocytes had undergone appropriate maturational changes and had reached metaphase II of meiosis to be ready for successful fertilization.

The serum oestradiol-17β values recorded during the follicular phase reached levels four- to six-fold that recorded at the pre-ovulatory peak of spontaneous ovulatory cycles (Kerin 1982) and such a response would carry a significant risk for both multiple pregnancies and hyperstimulation syndrome of women undergoing ovulation induction without in-vitro fertilization. However, during in-vitro fertilization, the generation of several mature oocytes to achieve a number of embryos is considered of significant advantage in improving the pregnancy rate (Yovich *et al.* 1984*b*) as it appears that only 40% of embryos generated have the potential to implant successfully (Yovich *et al.* 1984*d*). No patients developed hyperstimulation syndrome during the series studied, but subsequently one patient has experienced moderate abdominal distension with ovarian cysts in the luteal phase and detectable ascites. She had previously experienced this during a routine ovulation induction using clomiphene citrate combined with hCG injections to trigger ovulation and support the luteal phase. It is assumed that the relatively low incidence of hyperstimulation relates to the aspiration of follicular contents at the time of oocyte recovery.

We have previously published luteal phase data showing that oestradiol-17β and progesterone declined significantly after day 24 (day 10 of the luteal phase) in non-conception in-vitro fertilization cycles (Yovich *et al.* 1984*c*). Those patients given hCG support during the luteal phase had higher oestradiol-17β and progesterone levels with the latter rising further in the late luteal phase. Patients destined to abort demonstrated falling oestradiol-17β and progesterone levels after day 30. The effect was most marked in those given MPA during the luteal phase as they also had very low oestradiol-17β and progesterone levels throughout that phase. We have previously discussed the significant luteotrophic effect noted with hCG support regimens and an apparent luteal suppressant action of MPA (Yovich *et al.* 1984*c*). The delayed and retarded rise of β-hCG in those patients who subsequently aborted, supports the view we proposed that blighted ova arising in this in-vitro fertilization programme may have come from embryos trying to implant within a poor luteal hormonal environment. However, the data is not conclusive and the possibility that a deficient embryo factor may fail to provide satisfactory stimulation of the corpus luteum should be considered. No difference was noted in the pregnancy rate with either hCG or MPA luteal support regimens but the outcome appeared better in that fewer abortions occurred with hCG support. A tentative argument is that an inadequate steroidal environment limits trophoblast development by the embryo which then provides a less than optimal stimulus for further steroid output by the corpus luteum. A cycle is established which leads to failure of normal embryo development but which may be reversible by the timely use of hCG support injections to improve corpus luteal steroid output until the embryo is capable of stimulating the corpus luteum itself by endogenous hCG. We suspect that the markedly elevated progesterone values noted from the mid-luteal phase is an important feature for the successful implantation of pregnancies from in-vitro fertilization. Such values represent at least a three-fold increase from that noted with spontaneous, unstimulated non-in-vitro fertilization conceptions (Hull *et al.* 1982), but the earlier entry of embryos into the uterine cavity with in-vitro fertilization may create a special requirement for higher luteal progesterone levels. In this regard knowledge of the earlier luteal phase progesterone levels would be interesting to assess their possible relevance to successful embryo implantation.

During the first trimester of successful pregnancies, β-hCG levels continue to rise steadily, peaking at around 70 000 i.u./l between weeks 9 and 10. Thereafter values decline until week 14, plateauing at around 20 000 i.u./l. This pattern is not dissimilar to reports of pregnancies arising spontaneously (Kosasa 1981).

Those patients given MPA after pregnancy had been diagnosed (because of threatened abortion) did not demonstrate any significant differences in progesterone, oestradiol-17β or β-hCG levels if the pregnancy was progressing successfully (Table 1). In the first successful in-vitro fertilization pregnancy arising from this programme, MPA was given during the luteal phase and re-started after a short break during the early weeks of pregnancy when threatened abortion and declining progesterone levels were noted; it was felt that progestogen support therapy may well have salvaged that pregnancy. However, declining progesterone levels have not been seen in any of the subsequent ongoing pregnancies in this series. A useful therapeutic role for MPA support in early pregnancy cannot be concluded from this short series which tends to suggest that those pregnancies threatening to abort, with hormonal levels within the expected range for ongoing pregnancies, will continue to develop. The role of progestogen support therapy can only be assessed by a controlled study.

The trend to lower mid-luteal prolactin levels in the aborting group may be relevant in reflecting a failure of secretion from the decidual stromal cells which has been proposed as an important prerequisite for the successful implantation of the embryo (Maslar *et al.* 1980). An alternative explanation is that the observation may simply reflect inadequate decidualization of the endometrium which is progesterone-dependent as prolactin production can be increased progressively in decidual stroma by exogenous progesterone (Riddick *et al.* 1983)

From the end of the luteal phase oestradiol-17β and progesterone continued to rise for a further week, subsequently declining to mean plateau levels of 6488 (SEM 1066) pmol/l for oestradiol-17β and 196 (SEM 35) nmol/l for progesterone until week 12. At that stage oestradiol-17β levels begin to rise reaching mean levels of 17 357 (SEM 6148) pmol/l by week 16 and progesterone also rises after an initial decline to reach 231 (SEM 37) nmol/l by week 16. The rise in steroid output from the late first trimester into the mid-trimester is undoubtedly a reflection of placental development and the changeover from combined ovarian plus trophoblast secretion to essentially placental production (Csapo *et al.* 1972).

Previous reports have shown a steady increase in plasma progesterone values throughout the first trimester of normal pregnancies, rather than the plateau effect shown here. In a study by Radwanska *et al.* (1978), plasma progesterone levels ranged from 31·8 to 171·7 nmol/l (mean 81·1, SD 31·8 nmol/l) from 6 to 12 weeks gestation The levels in our study were higher throughout the early weeks and may reflect continuing progesterone output from hyperstimulated ovaries. It is likely that a steady decrease in ovarian output was matched by trophoblast secretion masking the continuous rise which one might find if only a single corpus luteum were present in the ovary. The apparent decline in progesterone levels from weeks 12 to 14 before the mid-trimester rise may also reflect the end stage of ovarian secretion. It was not observed with oestradiol-17β, possibly because placental production was already occurring in large enough quantity to mask the effect.

The technique of in-vitro fertilization has provided a uniquely abnormal milieu for the generation of human pregnancies. The ovarian stimulation programme leads to abnormally high levels of oestradiol-17β and progesterone (two- to three-fold that expected during spontaneous conceptions arising during unstimulated cycles). These high levels are carried through into the luteal phase and early weeks of pregnancy. It was postulated by Edwards *et al.* (1980) that hyperstimulation of the ovaries led to a markedly abnormal luteal phase which was foreshortened in proportion to the level of conjugated oestrogens excreted in the urine. That was one of the reasons cited for pursuing the techniques in unstimulated ovarian cycles and indeed their historic first successful pregnancy was achieved following the recovery of the single oocyte in a natural cycle (Steptoe & Edwards 1978). However, further experience with stimulated schedules using clomiphene citrate, hMG or combinations of the two have indeed shown that there is greater efficiency in generating in-vitro fertilization pregnancies following ovarian stimulation (Trounson *et al.* 1981; Speirs *et al.* 1984; Garcia *et al.* 1983). Abnormal luteal function has been well described following hMG/hCG induced ovulation (Olsen *et al.* 1983) but from the reports available to date, it remains uncertain if luteal phase support therapy improves the pregnancy rate, although it was noted in one study that the abortion rate was less following hCG support during the luteal phase (Yovich *et al.* 1984*c*). It has previously been noted in cycles stimulated with hMG or human pituitary gonadotrophin in non-in-vitro fertilization programmes for infertility therapy, that hCG support injections during the luteal phase improves the rate of successful pregnancies (Brown *et al.* 1980).

Concern has often been expressed that the techniques applied for in-vitro fertilization might generate abnormal embryos and cause fetal abnormalities. The exposure of the maturing oocyte to very high levels of sex steroids during the follicular phase and the implanting embryo during the luteal phase and early pregnancy requires consideration of the possibility of fetal abnormalities as such have been reported with the use of synthetic steroid and steroid-like drugs (Herbst *et al.* 1972; Levy *et al.* 1973; Janerich *et al.* 1974; Wilkins 1960; Aarskog 1979). The 22 infants delivered in this series were all perfectly normal and have been included in a long-term developmental assessment project which has so far revealed no abnormal features. Of 112 infants born following in-vitro fertilization in Australia to the end of July 1983 (Speirs *et al.* 1984), only one infant displayed an abnormality—that of a cardiac lesion in one twin (Wood *et al.* 1982). The vast majority of those pregnancies followed ovarian stimulation suggesting that high endogenous circulating steroid levels are unlikely to harm the developing embryo. Such conclusions are consistent with reported results of gonadotrophin therapy for ovulation induction which does not lead to increased congenital malformations or abnormal postnatal development even though hyperstimulation is reported in 3·6% to 7·8% of cases (Lunenfeld & Insler 1978*a*). Similarly, clomiphene citrate therapy for ovulation induction does not appear to cause fetal abnormalities (Lunenfeld & Insler 1978*b*) and the proportion exhibiting hyperstimulation is much less than for gonadotrophin.

In conclusion, this study reports the hormonal changes during the follicular phase, luteal phase and the first 16 weeks of pregnancy for conceptions arising from in-vitro fertilization where ovarian stimulation is a feature of the programme. Steroid hormone changes in response to luteal support therapy are noted, and it was found that pregnancies which subsequently aborted could be predicted by delayed and retarded β-hCG elevations combined with reduced oestradiol-17β and progesterone output in the late luteal and early pregnancy stages

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Reduced in-vitro fertilization of human oocytes from patients with raised basal luteinizing hormone levels during the follicular phase

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Summary. A series of 62 women were managed in the University of Western Australia/PIVET Laboratory in-vitro fertilization programme. In 60 of them follicle growth was stimulated with clomiphene citrate with or without additional human menopausal gonadotrophin (hMG) and in two with hMG alone. Follicles were aspirated at laparoscopy following an hCG trigger injection and occasionally following a spontaneous luteinizing hormone (LH) surge. Oocytes were inseminated with $0 \cdot 5 \times 10^5$–10^5 sperm/ml 3–6 h later. A significant reduction ($P<0 \cdot 001$) in the fertilization rate of mature oocytes was observed in those patients whose basal serum LH values were >1 SD above the mean. Fifty-nine women subsequently had embryo transfer and of 10 clinical pregnancies, none occurred in those with elevated LH values. Reduced fertilization may be a reflection of premature oocyte maturation or ageing. This may have clinical implications in the management of some patients with unexplained infertility.

During the monitoring of follicular development for in-vitro fertilization, clinical attention is focused on the physical enlargement of individual follicles detected by ultrasound and increasing steroidogenic activity, measured by serum oestradiol-17β (Yovich *et al.* 1984*a*). The growth phase is also a period of intense metabolic activity and cytoplasmic development within the oocyte (Tsafriri 1978). Indeed, many of the proteins and much of the RNA required during early embryonic cleavage stages are thought to be generated in the oocyte both before and following the initiation of meiosis (Biggers & Powers 1979; Motlik *et al.* 1980). Since steroid hormone production within the follicle is under the control of gonadotrophins, any alterations in the balance of the control mechanisms governing follicle growth may also be expected to indirectly affect oocyte function. There is some evidence, for instance in sheep, that impaired fertilization and embryo growth may result from atypical gonadotrophin levels (Moor & Trounson 1977).

Luteinizing hormone (LH) has several important roles in follicle development. The more important are those associated with the mid-cycle surge. These include initiating the mechanism leading to follicle rupture (Strickland & Beers 1979), stimulating luteal progesterone secretion (Katz 1981), activating the oocyte to resume meiosis (Jagiello *et al.* 1975) and promoting the expansion of the cumulus oophorus and its detachment from the granulosa layer of the follicle wall (Dekel *et al.* 1979). During the follicle growth phase, LH also appears to be important in promoting the synthesis of androgens by thecal cells, which, under the influence of follicle

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stimulating hormone (FSH), are later converted to oestradiol-17β in the granulosa cells (Katz 1981). During this period serum levels of LH are normally low (Baird *et al.* 1976).

Abnormal LH secretion in women has been reported in association with polycystic ovarian disease where FSH is normal and basal LH is usually elevated (Baird *et al.* 1976). During the intensive monitoring of women treated for infertility by in-vitro fertilization and ovulation induction we have observed elevated basal LH levels in patients without additional stigmata of polycystic ovarian disease and who had ovaries of normal size and appearance at laparoscopy. Patients with polycystic ovarian disease are known to have reduced or absent ovulation and although many conceive following ovulation induction, the fertilization potential of oocytes derived from patients with elevated serum LH has not been fully investigated.

The development of in-vitro fertilization, embryo culture and embryo transfer procedures have provided an opportunity to assess gamete quality and the fertilization potential from patients with various clinical and hormonal states. The results presented in this report suggest that oocytes obtained from the pre-ovulatory follicles of women with elevated LH levels have impaired fertilization ability and that those embryos which do occur are less likely to implant successfully.

Patients and methods

This study was based on 62 consecutive aspirations carried out between November 1982 and May 1983 at the PIVET Laboratory/University of Western Australia in-vitro fertilization programme (Yovich *et al.* 1984*a*). Of the 62 patients admitted to the study 55 had absent, blocked or non-functional fallopian tubes (one had defined polycystic ovarian disease), three had endometriosis, and four had oligospermic husbands. Procedures for follicle stimulation and patient management were similar to those described elsewhere (Stanger & Yovich 1984; Yovich *et al.* 1984*a*, *b*). Briefly, follicle growth was stimulated with clomiphene citrate (Clomid, Merrell Dow Pharmaceutical Inc., Cincinatti, Ohio, USA), 150 mg given daily on days 2 to 6 of the menstrual cycle, in 60 patients and 11 of them received additional maintenance of follicular growth with three ampoules of human menopausal gonadotrophin (hMG) (Pergonal, I.F. Serono, Rome, Italy) administered daily between days 6 and 11. Generally, supplementation was given to those patients who had previously demonstrated a poor response to clomiphene citrate (fewer than two mature oocytes recovered at laparoscopy). The two remaining patients had follicle development stimulated solely with hMG (three ampoules daily) administered between days 3 to 12. Follicle growth was monitored from day 8 to the day before aspiration by combined early morning ultrasound tracking of follicle diameter (mean of three diameters), cervical score and hormonal assays (oestradiol-17β, progesterone and LH) from serum collected before the hMG injection. As an indication of follicle maturity, the mean number and size of follicles present and the serum oestradiol-17β concentration on the day of either ovulation induction or beginning of the LH surge were recorded in relation to the patient's mean LH level.

The patients were admitted for ovulation induction when the average size of the leading follicles was ≥18 mm and the serum oestradiol-17β concentration was about 1500 pmol/l per major follicle. Before the intramuscular injection of 5000 units of human chorionic gonadotrophin (hCG), a blood sample was taken to ensure LH levels were still within the basal range. In 49 patients not demonstrating a surge in LH, laparoscopy was timed at 36 h after the hCG injection. In 11 patients whose serum LH had risen to levels greater than 2 SD above the mean basal level at the time of hCG, laparoscopy was between 30 and 34 h after the hCG injection and the two patients whose routine morning sample indicated the early stage of a spontaneous LH surge, were laparoscoped 33–36 h after estimated onset without hCG administration. Patients who were considered to be in an advanced stage of spontaneous LH surge were not included in this study.

Fertilization in vitro and embryo development

Oocytes were collected by laparoscopic follicle aspiration into modified Tyrode's medium (Whittingham 1971; Quinn *et al.* 1984) containing 15% heat-inactivated maternal serum. The oocyte enclosed in the cumulus mass was incubated for 3–6 h in 5% CO_2, 5% O_2, and 90% N_2 before the addition of spermatozoa at a concentration of between $0{\cdot}5\times10^5$ and 10^5 spermatozoa/ml. Fertilization was recognized

16–20 h later by finding two pronuclei in the cytoplasm of the oocyte and usually a second polar body in the perivitelline space. Embryos and oocytes without pronuclei were returned to 1 ml of fresh culture medium and incubated overnight before embryo transfer 40–48 h after aspiration. Immature oocytes identified at the time of ovum collection with a small incompletely expanded cumulus oophorous enclosed by a tight and dense coronal cell layer were excluded from this study. No attempt was made to re-inseminate unfertilized oocytes. In this series, cleavage was not observed in any embryo failing to demonstrate pronuclei on the day after insemination.

Hormone assessment

LH was assessed in the serum of all patients within 2 h of collection (08.00 hours) by radioimmunoassay. LH was isolated by rabbit anti-human LH antiserum, separated by goat anti-rabbit α-globulin antiserum, and compared to a standard curve of human LH (0–200 i.u./l) standardized against the WHO pituitary reference preparation (IRP 68/80) (Diagnostic Products Corporation, Los Angeles, California). The limit of this assay is reported to be 2 i.u./l. The intra-assay and inter-assay coefficients of variation were <3·6% and 8·3% respectively. Cross-reactivity with FSH was <4·5% and with TSH <3·7%. Progesterone was also estimated in the same serum sample using solid phase radioimmunoassay (Coat-A-Count, Diagnostic Products Corporation, Los Angeles, California).

Analysis of data

LH and progesterone data in the study were drawn from all daily estimations obtained before either the hCG injection, where no endogenous surge of LH was observed, or before a detectable rise in LH associated with the onset of the surge. Care was taken not to include any estimations associated with the LH surge. In the 49 patients whose LH was at basal levels before the hCG injection, this was uncomplicated. In the 13 patients whose LH had risen before admission, the value for that day was omitted from the calculations. The effect of the type of follicle stimulation on the daily serum LH concentration and the change in concentration with time were both examied by one-way analysis of variance of the raw LH data (Zar 1974). An overall group mean and standard deviation (SD) were then calculated from the data pool. For each patient, mean follicular phase LH and progesterone levels were obtained. Based on this, each patient was allocated to one of the following three categories: group 1, LH level <1 SD below the mean value; group 2, LH level within 1 SD of the mean; and group 3, LH level >1 SD above the mean.

Individual fertilization rates and cleavage rates were calculated within each group and the totals compared by χ^2 analysis using a standard 2×2 contingency table.

The rates in groups 1 and 2 were first tested for homogeneity before being combined and compared with the rate in group 3 (Zar 1974).

Results

The overall mean follicular phase serum LH value of the 62 patients was 13·9 i.u./l (SD 6·69) (Fig. 1). There was no significant difference (P>0·20) in the mean LH level between those patients receiving clomiphene citrate (14·2 i.u./l) and those receiving clomiphene citrate and hMG (13·8 i.u./l) (Fig. 2). In both groups, the LH concentration fell significantly (P<0·05) between days 8 and 12 of the follicular phase (Fig. 2). Nine patients had a mean LH level >1 SD above the mean.

The proportion of mature oocytes which fertilized and the subsequent proportion of fertilized ova which proceeded to cleaving embryos for the three groups are shown in Table 1. In all, 153 mature oocytes were collected providing an average yield of 2·5 oocytes per patient. The fertilization rate was >84% for the two groups whose follicular phase serum LH level was not >1 SD above the mean. However, the fertilization rate in the nine patients in group 3 (LH level >1 SD above the mean) was significantly reduced (P<0·001). In addition, fewer of the fertilized oocytes proceeded to cleavage (P<0·01).

Of the 62 women admitted for follicle aspiration, 59 subsequently had embryo transfer. Two of the three patients who failed to produce any fertilized oocytes came from group 3. Ten patients have subsequently had pregnancies confirmed by rising β-hCG levels and positive ultrasound confirmation of an intrauterine gestational sac.

Little difference existed in the maturity of the follicles generated in the three groups as indi-

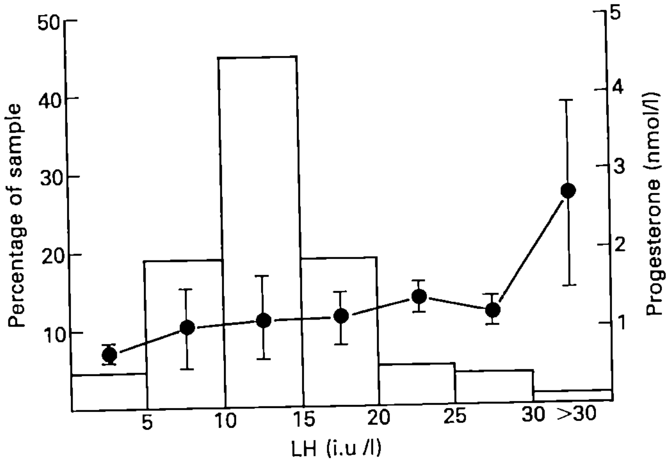

Fig. 1. Distribution of individual mean serum LH concentration (histogram) and the corresponding mean progesterone concentration (●) in 62 patients admitted for in-vitro fertilization. Both hormones were averaged over the whole follicle growing phase before the mid-cycle LH surge. Vertical bars show the SEM values.

cated by the number and diameter of the follicles and their oestrogen production (Table 2). The higher oestrogen and progesterone levels noted in group 3 were attributed to the administration of hMG since proportionately more patients in group 3 required this supplementation. The relation between serum LH and progesterone levels during the phase of maximum follicle growth is shown in Fig. 1. The progesterone level remained low at all LH levels except in those patients whose LH exceeded 30 i.u./l. Applying the same criteria as with LH levels (i.e. mean±1 SD), six patients had a mean progesterone level >1·84 nmol/l (1 SD above the mean) throughout the follicular phase. Of these, four had mean LH levels ≤20·6 i.u./l and their oocytes fertilized and developed normally (Table 3) One of the patients conceived following embryo transfer. However, in seven patients whose LH level was elevated without a concurrent increase in progesterone, the fertilization rate of oocytes was reduced to 57%. Where both hormone levels were raised (two patients only), only one of eight ova was fertilized. Overall there was no significant difference in the fertilization rate between the groups with high or low progesterone levels ($0{\cdot}05<P<0{\cdot}1$).

The reduced fertilization rate in group 3 was analysed against the follicle-stimulation regimen and ovulation-induction trigger (Table 4). There was no significant association with the follicle-stimulation regimen but none of the women had a spontaneous LH surge. However, the observation did not reach significance in this small series (χ^2, ν 1:1·5, $P>0{\cdot}01$). None of the 10 pregnancies occurred in group 3, nine occurred in women who had hCG alone and the tenth had an LH surge with hCG augmentation.

Discussion

The average range of basal serum LH estimated in this study agrees well with previous reports (Kerin *et al.* 1981; Djahanbakhch *et al.* 1981). The administration of hMG, which contains equal amounts of FSH and LH, to sustain follicle growth made no significant difference in the amount of LH detectable in serum when compared to the group given clomiphene citrate only. In unstimulated cycles, LH is generally observed to remain relatively unchanged from day 1 (Faiman *et al* 1976). Irrespective of the type of stimulation, the LH values in this group of patients fell significantly ($P<0{\cdot}05$) from a mean of 17·5 i.u./l on day 8 to 11·6 i.u./l on day 12 (Fig. 2). The decrease most likely reflects a downturn in gonadotrophin secretion following both the period of sustained clomiphene citrate exposure and the rising oestradiol-17β levels. The effect of clomiphene citrate on LH secretion has been reported to be less than on FSH during the early part of the follicular phase (Vandenburg & Yen 1973) with an increase in responsiveness as the stage of the cycle advances. The

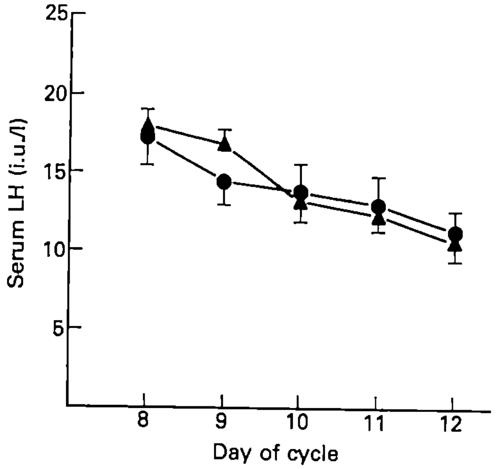

Fig. 2. Mean serum LH levels between days 8 and 12 of the menstrual cycle in women stimulated with either clomiphene citrate (●) or clomiphene citrate plus hMG (▲). Vertical bars show the SEM values.

patients described here all received clomiphene citrate from days 2 to 6 and it is therefore unknown if the pattern of LH secretion would be similar in a regimen where clomiphene citrate was given later.

The elevated basal follicular LH value found in eight patients in group 3 was somewhat unexpected since seven of them were included in the programme because of a known tubal disorder and one patient because her husband had moderate oligospermia. Only one patient in this group was known to have elevated basal LH levels consistent with a clinical diagnosis of polycystic ovarian disease. In the investigations of patients for selection for in-vitro fertilization, we have not routinely monitored gonadotrophin levels unless a co-existing ovulation disorder was indicated from the menstrual history, hence we do not have prior information about LH levels in this group.

The data suggest that there may be a relatively small group of patients who have LH values in excess of the normal range during stimulated cycles. It would appear that oocytes from these patients have a reduced ability to be fertilized. The correlation between high basal levels of LH and reduced fertility became apparent when two patients with very high LH values (>30i.u./l) and elevated progesterone levels (Table 3) failed to generate the anticipated number of embryos even though eight oocytes were collected; the cumulus masses at collection were fully expanded but dark in appearance. The majority of the oocytes, when examined 16 h after insemination, did not demonstrate two pronuclei and a normally light-brown translucent cytoplasm. The majority of the ova, whilst appearing spherical in shape, were darker in colour although showing no clear signs of degeneration. In some oocytes, a polar body was visible. None of the oocytes contained a germinal vesicle, indicating the resumption of meiosis had been initiated. Furthermore, the quality of the few embryos which were generated were clearly inferior to those routinely developed in the programme displaying excessive fragmentation and asymmetrical cleavage. These features suggested that the oocytes were in the early stages of atresia.

The reduced fertilization cannot be attributed to poor follicular development since all patients in group 3 had follicle growth and oestradiol-17β production indistinguishable from that in the other two groups (Table 2). The progesterone levels appeared similar in all groups (Table 2) and overall were independent of LH con-

Table 1. The relation between basal luteinizing hormone (LH) concentrations and the fertilization of human ova *in vitro*

Group	Basal serum LH (i u./l)	Number of patients	Pronuclear ova/ inseminated ova		Cleaving embryos/ fertilized ova		Number pregnant
			n/n	(%)	*n/n*	(%)	
1	<7·3 (mean−1 SD)	8	15/17	(88)	14/15	(93)	2
2	7·3–20·6 (mean±1 SD)	45	96/107	(90)	87/96	(91)	8
3	>20·6 (mean+1 SD)	9	13/29	(45)	8/13	(61)	0
Total	—	62	124/153	(81)	109/124	(88)	10

Table 2. Hormonal and follicle characteristics on the day of hCG administration in relation to mean basal luteinizing hormone (LH) levels

Characteristic	Basal LH concentration (i.u./l) <7·3	7·3–20·6	>20·6
Number of patients	8	45	9
Follicles >15 mm in diameter			
Mean number	2·2 (0·36)	2·5 (0·37)	2·7 (0·43)
Mean diameter (mm)	19·2 (0·24)	19·3 (0·57)	18·9 (0·21)
Mean oestradiol-17β (nmol/l)	3·1 (0·99)	3·7 (0·28)	4·5 (0·88)
Mean progesterone (nmol/l)	0·8 (0·23)	0·9 (0·25)	1·6 (0·69)

SEM values are shown in parenthesis.

centration, except where the latter was grossly elevated (Fig. 1).

In attempting to explain the reduced fertilization rate of oocytes obtained from patients with elevated serum LH levels two possibilities were considered likely. The first was that LH acted directly to initiate the resumption of meiosis at a premature stage of follicle development resulting in aged oocytes at aspiration. The second was that levels of steroid hormone produced by the growing antral follicle were sufficiently altered to interfere with the normal development of the oocyte. At present neither possibility can readily be assessed.

Even though LH is the hormone responsible for triggering the resumption of meiosis in the oocyte, it is only known to do so during the surge via an indirect action by increasing intrafollicular cyclic AMP levels (Hunzicker-Dunn *et al.* 1979). Two mechanisms have been proposed. One is the removal of a low-molecular-weight inhibitor of oocyte maturation (OMI) thought to be produced by the granulosa tissue (Channing 1979) and which is lost following LH stimulation (Tsafriri & Linder 1978). More recently, it has been suggested that reduced oocyte fertilization occurs when high levels of OMI persist in the antral fluid after LH activation of ovulation, presumably where the follicle is immature (Channing *et al.* 1983). If this is the case, could the reverse also occur when sustained LH exposure during the follicle growth phase leads to a premature loss of OMI in mature follicles without initiating ovulation? The other possible mechanism involves disruption of the intracellular coupling between the oocyte and the coronal cells during cumulus expansion. While the relationship between cumulus expansion, cellular

Table 3. Relation between serum luteinizing hormone (LH) and progesterone and the fertilization rate of human ova *in vitro*

	Basal LH concentration (i.u /l)					
	≤20 6†		>20·6		Total	
Progesterone	No. of patients	Fertilization rate* *n*/*N* (%; range)	No of patients	Fertilization rate *n*/*N* (%; range)	No. of patients	Fertilization rate *n*/*N*
≤1·84‡	49	100/113 (88; 0–100)	7	12/21 (57, 0–75)	56	112/134
>1·84	4	11/11 (100, —)	2	1/8 (12; —)	6	12/19
Total	53	111/124	9	13/29	62	124/153

*The fertilization rate is the number of mature ova with pronuclei (*n*) divided by the number of mature ova inseminated (*N*).

†Value represents the mean+1 SD serum LH concentration

‡Value represents the mean+1 SD serum progesterone concentration.

Table 4. Stimulation and ovulation regimens of patients with normal and elevated basal serum luteinizing hormone (LH) concentration

Basal LH concentration (i.u./l)	Stimulation regimen			Ovulation regimen		
	Clomiphene	Clomiphene +hMG	hMG	LH Surge	LH Surge +hCG	hCG
≤20·6	43	8	2	2	11	40
>20·6	6	3	0	0	0	9
Total	49	11	2	2	11	49

communication and oocyte meiotic maturation is unclear in women, in the mouse, cumulus expansion and initiation of oocyte maturation appears linked and controlled by both LH and FSH (Eppig 1981, 1982*a*, *b*). It is suggested that elevated LH levels during follicle growth may trigger meiotic activity in the oocyte either by affecting OMI levels or by altering the cumulus–coronal cell–oocyte axis without a concommittant induction of luteinization or ovulation. In our study the net effect would therefore be that some oocytes may spontaneously resume meiosis well before the administration of hCG such that by the time of aspiration the oocyte has passed beyond its fertilizable life.This might be assessed by the examination of oocytes collected from growing follicles not stimulated with hCG.

Since LH is thought to stimulate steroidogenic activity in the thecal tissue of the growing follicle (Katz 1981), sustained exposure to elevated LH levels could potentially result in an altered hormonal environment within the antrum. This may be the more relevant hypothesis since, in isolated mouse follicle experiments, high progesterone levels induce oocyte atresia (Tyler & Collins 1980) and increase the number of meiotically inactive oocytes (Tyler *et al.* 1980; Smith & Tenny 1980). Reduced fertilization rates of ovine oocytes and abnormal embryo development *in vivo* after follicle growth *in vitro* has been shown in the presence of elevated gonadotrophin (Moor & Trounson 1977) and steroid levels (Moor *et al.* 1980).

When the relation between basal serum LH, progesterone and the fertilization of human ova was examined, no evidence was obtained to support a primary role of progesterone in reduced fertilization of human ova *in vitro* (Table 3). This of course does not negate its involvement since a compounding influence with LH may exist as illustrated by reduced penetration when both factors were elevated. As indicated by the error bars in Fig. 1, progesterone levels of >1·84 nmol/l may be found in patients with very low as well as normal LH values. However, markedly elevated progesterone values (>2·8 nmol/l) were only found where the mean LH concentration exceeded 30 i.u./l.

While care needs to be exercised in interpreting results obtained by association rather than by controlled experimentation, the data presented here suggest that as a result of excessive LH secretion, the capacity of the oocyte to be fertilized and develop normally may be diminished and as such warrants further investigation. At a clinical level, the presence of basal LH values >1 SD above the mean may represent a potential cause of infertility. This is apparent despite adequate follicle growth according to follicle size and oestradiol-17β production. While a value of 20·6 i.u./l was chosen to represent a division between groups 2 and 3, the numerical value is of less importance than the distribution of patients relative to the mean. This may vary with the type of assay and between laboratories. Even within an elevated group, variation in the fertilization rate may represent differences in the relative sensitivity of the follicles to LH and possibly in the level of biologically active gonadotrophin. Efforts to reduce basal LH levels, for instance by the use of LHRH antagonists (Flemming *et al.* 1984), may prove to be beneficial if FSH can be given to support follicle growth. Elevated LH and progesterone levels are classically associated with polycystic ovaries and anovulation. Although all patients in this series, except one, had regular menses and no other stigmata of polycystic ovarian disease, those patients with elevated LH may reflect one edge of a much broader spectrum. Levels of FSH and androgens such as testosterone were not estimated in these samples but would be of interest in this regard.

Acknowledgments

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The treatment of cervical intraepithelial neoplasia by laser vaporization

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Summary. Of 711 women with cervical intraepithelial neoplasia (CIN) treated by laser vaporization 675 (95%) remain colposcopically and cytologically free from disease after a median follow-up of 20 months. Thirty-six patients needed other forms of treatment to eradicate suspected residual disease. One patient presented with invasive carcinoma of the cervix 34 months after treatment with the carbon dioxide laser. It is concluded that in selected cases laser vaporization is an effective method of treating pre-invasive disease of the cervix.

In England and Wales the incidence of cervical intraepithelial neoplasia (CIN) has more than doubled in the last decade (Draper & Cook 1983) and the greatest increase has occurred in young women in whom surgical treatment may reduce fertility.

The colposcope is now used widely. With it the upper and lower limits of the cervical lesion can be demonstrated in over 75% of young women who have cervical intraepithelial neoplasia (Singer & Walker 1982) and in such patients hysterectomy is over-treatment, unless indicated for other reasons, and even removal of a cone may jeopardize cervical function Other methods of treating CIN of definable extent have been assessed, and success rates between 87% and 98% are claimed for cryotherapy (Richart *et al.* 1980), cold coagulation (Duncan 1981), laser vaporization (Baggish 1980; Burke 1982; Anderson 1982; Evans & Monaghan 1983), or coagulation electrodiathermy (Chanen & Rowe 1983; Woodman *et al.* 1985).

Women who attended the colposcopy clinics at the Birmingham and Midland Hospital for Women between 1976 and 1982 and were found to have CIN were managed in a variety of ways. In this period a total of 1550 were treated, 652 (42%) by removal of a cone, 140 (9%) by coagulation electrodiathermy, 47 (3%) by hysterectomy and 711 (46%) by laser vaporization. In this paper we present and comment on our experience with this last form of treatment.

Patients and methods

All patients had been referred for investigation of cytological abnormality; all were assessed colposcopically and material for histological examination obtained by directed punch biopsy.

Patients were treated with the CO_2 laser if colposcopic examination could define both limits of the transformation zone, histological confirmation of CIN had been obtained and invasive disease excluded. The whole of the transformation zone was destroyed using either a Cathetron, Coherent or Sharplan laser at a power density of 20 W/cm^2, with intra-operative colposcopic control. During the first 6 months of the study the zone was vaporized to a depth of

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only 2 mm, but when it was realized that this failed to eradicate CIN consistently the depth of destruction was increased and during the last 5 years we have attempted to destroy tissue to between 5 and 7 mm.

A total of 711 patients were treated by laser vaporization, 663 as out-patients. The other 48 were admitted to hospital for general anaesthesia, in 18 pre-operative colposcopic assessment showed the transformation zone to cover an unusually extensive area of the cervix or to extend to the vagina; in eight excessive bleeding prevented the completion of treatment in the out-patient department, two of these patients requiring immediate admission for control of haemorrhage; in five, treatment was discontinued because of the patient's discomfort and eight others were considered unlikely to tolerate out-patient treatment; five patients were admitted for assessment under anaesthesia when out-patient colposcopy failed to define the limits of the transformation zone; four were admitted because they required general anaesthesia for other gynaecological procedures.

The patients were re-examined 4 and 10 months after treatment using cytology and colposcopy. Those without evidence of disease were then followed up by annual clinical and cytological examination, 88% at the Birmingham and Midland Hospital for Women and 12%, who lived at a distance, by their general practitioners.

Results

The mean age of the patients was 29 years (range 17–51). There were 142 patients with mild dysplasia (CIN 1), 153 with moderate dysplasia (CIN 2) and 416 with severe dysplasia or carcinoma *in situ* (CIN 3).

Follow-up (Table 1)

Of the 711 patients, 700 were assessed colposcopically after treatment. While 645 women are known to have had a cervical smear taken within the 12 months preceding this report, 66 (10%) were lost to long-term cytological follow-up; six failed to return immediately after treatment, nine after the postoperative assessment at 4 months, 18 after that at 8 months, 23 after 1 year, nine after 2 years and one after 3 years. No patient known to have abnormal cytology has been lost to follow-up.

Table 1. Cytology follow-up

Duration (months)	Number of patients (%)	Number subsequently defaulting
4	705 (99)	15*
8	585 (82)	18
12	353 (49)	23
24	295 (41)	9
36	147 (20)	1
48	48 (6)	0
60	8 (1)	0
		66

* Six patients failed to return after treatmment

Outcome after laser vaporization

Pre-treatment histology. Of the 142 patients with CIN 1, 140 (99%) remain colposcopically and cytologically free of disease; 145 (95%) of 153 with CIN 2, and 390 (94%) of 416 with CIN 3.

Depth of destruction. Laser vaporization to a depth of <4 mm failed to eradicate disease in 97 (63%) of 154 treatment applications. In contrast a single laser vaporization to a depth of >5 mm failed in only 64 (10%) of 645 treatment applications.

Duration of follow-up (Fig. 1). Residual disease was suspected at the time of the first postoperative cytological or colposcopic assessment in 120 patients; in 30 patients who appeared cured at this first postoperative examination residual disease was found at the second postoperative assessment. In seven patients this was found after an interval of at least 12 months after treatment during which cytological and colposcopic examination had revealed no abnormality, and in four this interval lasted more than 2 years.

Outcome following failure of a single laser vaporization

Successfully retreated by laser. Ninety-seven patients were found to have residual disease after laser vaporization to a depth of ≤4 mm, but 85 are now free from disease following a second more-effective treatment which destroyed tissue to >5 mm. Of 64 patients with residual disease after initial laser vaporization to a depth of

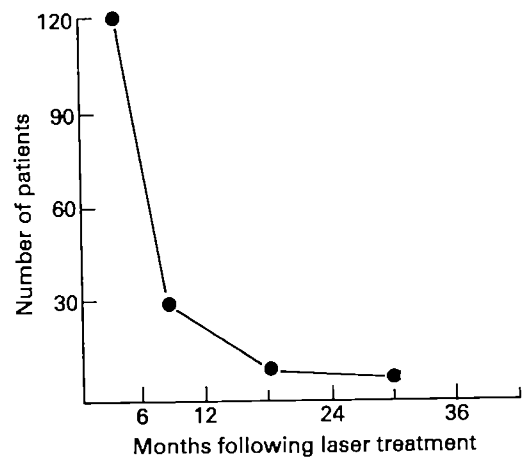

Fig. 1. Intervals to detection of residual disease following failure of one treatment application.

5–7 mm, 39 remain colposcopically and cytologically free of disease following further treatment, after a median follow-up of 16 months.

Laser failures. Thus, 36 patients had to be treated in other ways when residual disease was suspected after repeated laser vaporization, 26 by conization, four by hysterectomy, three by coagulation electrodiathermy and one by cryocautery; one patient had radiotherapy for invasive carcinoma; in one a colposcopically directed punch biopsy appears to have removed a small area of residual CIN. Histological confirmation of residual disease was obtained in 28 of these patients, but cone biopsy was negative in three as was examination of the cervix following hysterectomy in two others, all of whom had persistently abnormal cytological and colposcopic findings after laser vaporization. Two patients were found to have early stromal invasion defined according to the recommendation of the RCOG Study Group (1981)—i e. 'invasive buds are present either in continuity with an "in-situ" lesion, or apparently separated cells are not more than 1 mm from the nearest surface of crypt basement membrane'. These two and the patient with more advanced invasion are sufficiently disturbing to merit further attention.

Invasion following laser vaporization

Patient 1: Early stromal invasion. This patient was suspected on colposcopy of having CIN 3 and histological examination of a directed punch biopsy confirmed this. The abnormal transformation zone was then destroyed to a depth of 7 mm. A further biopsy taken 3 months later showed residual CIN 3 and the diseased area was destroyed to a depth of 1 cm. Colposcopic and cytological abnormality persisted and a cone was removed 12 months after the initial treatment; this revealed a focus of early stromal invasion.

Patient 2. Early stromal invasion. This patient too was suspected on colposcopy of having CIN 3 Histological examination of a directed punch biopsy revealed dysplastic squamous epithelium which could not be characterized further because the outer layers of the lesion were missing. A biopsy taken later at the time of laser treatment revealed CIN 3 with a focus of early stromal invasion. Histological examination of a cone cut 6 months after laser treatment revealed no residual abnormality.

Patient 3. Invasive carcinoma. Cytological examination of the cervix in this patient had revealed moderate dyskaryosis with features suggestive of human papilloma virus infection (HPV) on two occasions in the 12 months preceding her referral for colposcopic evaluation. This showed areas of leucoplakia and CIN with features consistent with HPV infection. Directed punch biopsies revealed CIN 1 on the anterior lip of the cervix and CIN 3 on the posterior lip. Laser vaporization of the whole transformation zone was performed to a depth of 7 mm. Cervical cytology at 2 and 6 months after treatment was reported as normal. Colposcopic examination of the cervix at 6 months revealed a small area of atypical epithelium consistent with HPV infection and unlikely to represent residual CIN. This area was not biopsied and no further colposcopic examination was performed as the cervical smear taken at this examination revealed no abnormality. Further cytological examinations at 12 and 24 months were reported as showing no abnormality. However, later review of these cytological preparations showed dyskaryotic cells. This patient presented to her general practitioner 34 months after laser vaporization with constipation and dyspareunia, following which she was found to have a stage IV squamous carcinoma of the cervix.

Discussion

Attention is increasingly being drawn to the use of destructive techniques in the treatment of CIN. Because the first use of the laser for this was relatively recent, there is no long-term follow-up, although early results from most major centres are encouraging. Our first patient was treated in 1977; the median follow-up period is 20 months.

Early in our study the depth of tissue destroyed was found to be important, and by trial and error it was concluded that we should aim for 5–7 mm (Jordan 1979). Anderson & Hartley (1980), measuring the depth of gland involvement, arrived at a similar conclusion. This is now generally accepted and most workers in the field recommend destruction to a depth of between 5 and 8 mm (Baggish 1980; Burke 1982; Evans & Monaghan 1983).

In our patients a single laser vaporization to a depth of 5–7 mm eradicated the lesion in 90% of patients: about half of those with residual disease were treated successfully by a further laser vaporization, an overall cure rate of 95%.

The management of early invasive malignancy is open to discussion, not only in the context of laser treatment. It has been suggested that what has loosely been called 'microinvasive' carcinoma can be separated into two stages, early stromal invasion with isolated foci penetrating less than 1 mm, and more advanced invasion, between 1 and 5 mm in depth; certain knowledge is lacking about which tumours in the second group can be treated by local excision and which need more radical methods. Early stromal invasion, under whatever name it has been known, has long been thought to be treated adequately by conization provided that the whole of the parent intraepithelial lesion is excised. Without doubt many small invasive foci can be dealt with by local destructive methods, including laser; indeed it is possible that some cases of CIN so treated have an unrecognized invasive component. At present, however, it does not seem to us justifiable to attempt to treat patients in whom early stromal invasion is suspected on punch biopsies with destructive techniques, for such specimens are too small to allow more advanced invasion to be excluded with certainty. Local treatment of early stromal invasion is safe if the parent intraepithelial lesion is completely removed: this can be shown when a larger specimen such as a cone is examined.

Follow-up is important. Although most of our patients with residual disease were discovered at the first follow-up at 4 months, and most of the remainder at 8 months, 11 were not suspected of having residual disease until more than 12 months after treatment, showing follow-up for a long term to be obligatory.

The development of invasive growth in one of our patients is disturbing, and those who oppose the use of destructive techniques give the danger of missing invasive carcinoma as a reason for treating CIN primarily by removing a cone or the uterus. Invasive disease, however, can and does occur after both conization and hysterectomy. Coppleson (1981) reviewed a large series of cases from the world literature and found that 18 out of 5442 cases (0·30%) of CIN treated by conization or amputation and 38 of 8854 cases (0·23%) treated by hysterectomy subsequently developed invasive carcinoma. Whatever method of treatment is used, invasive carcinoma will develop in a few patients; the single patient reported here does not discredit laser vaporization, but warns of the care needed in the selection of patients and in their adequate follow-up.

We conclude that provided that such conditions are followed, laser vaporization has proved in our hands to be an effective method of treating CIN. The conditions to be met before undertaking laser vaporization cannot be repeated too often: assessment must have been made by an experienced colposcopist who should see the entire lesion and transformation zone; invasive carcinoma must be excluded by biopsy, the result of which must be known before treatment is started; the colposcopist himself should carry out the destructive treatment and full cytological and colposcopic follow-up must be ensured (Jordan 1983). We also feel that if there is any suspicion that a glandular lesion, atypia or carcinoma *in situ*, is present operative treatment is preferable.

Despite the shortness of follow-up there is no reason to doubt that the excellent long-term results recorded in the past by those skilled in the use of diathermy and cryocautery will be reproduced with the laser. We believe that the precision with which it allows the lesion to be removed, the high proportion that can be treated in the out-patient department and the rapidity of healing with minimal post-operative fibrosis (Mylotte & Jordan 1982) gives laser vaporization advantages over those other techniques.

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Correlation between cytoplasmic steroid receptors and tumour differentiation and invasion in endometrial carcinoma

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Summary. The incidence and levels of cytoplasmic steroid receptors were studied in 155 endometrial carcinomas: oestrogen receptors (ER) were measured in all samples, progesterone receptors (PR) in 148 and androgen receptors (AR) in 118. Well-differentiated adenocarcinomas were significantly more likely to contain ER, PR and AR than were poorly-differentiated tumours, and mean values of ER and PR content were significantly higher in well-differentiated adenocarcinomas than in less-differentiated tumours. Receptor profiles in adenosquamous carcinomas and clear-cell carcinomas were similar to those in adenocarcinomas. Deeply invasive tumours were significantly less likely to be ER, PR or AR positive and, even when positive, such tumours had significantly lower mean levels of ER and PR. Poorly-differentiated tumours were significantly more likely to be ER-negative PR-positive than well-differentiated adenocarcinomas and adenosquamous carcinomas.

The study of sex steroid receptors in breast carcinoma has not only given a guide to prognosis, with oestrogen receptor (ER)-negative tumours being more likely to recur earlier and to be associated with a poorer survival than ER-positive tumours (Knight *et al.* 1977; Fletcher *et al.* 1978), but also has led to management programmes utilizing hormonal and chemotherapeutic regimens based on the receptor content of the primary tumour (McGuire 1979).

Since Brush *et al.* (1968) first demonstrated the binding of 17β-oestradiol to endometrial cancer cells, there have been several reports on the steroid receptor content of primary endometrial tumours. There is considerable debate as to the effect of tumour differentiation on receptor content. Most authors report a higher incidence and content of ER (Terenuis *et al.* 1971; Hahnel *et al.* 1979; Friberg *et al.* 1978; McCarty *et al.* 1979; Spona *et al.* 1979; Kauppila *et al.* 1982*a*) and progesterone receptor (PR) (Haukkamaa *et al.* 1971; Young *et al.* 1976; MacLaughlin & Richardson 1976; Pollow *et al.* 1977; Martin *et al.* 1979; Creasman *et al.* 1980; Kauppila *et al.* 1982*a*) in well-differentiated tumours compared with that in poorly-differentiated tumours. In contrast, there has been one report suggesting a reduced incidence of ER in well-differentiated carcinomas (Pollow *et al.* 1978), and two reports showing that tumour differentiation had no effect on ER (Crocker *et al.* 1974) or PR (Rodriguez *et al.* 1979). Many of these studies, however, have involved small numbers of patients.

The relation between invasion of the myometrium and endometrial cancer receptor content was analysed by Creasman *et al.* (1980) who found no association and by Kauppila *et al.* (1982*b*) who noted significantly lower mean ER and PR concentrations in tumours which invaded half or more of the myometrium.

Only two studies (Grilli *et al.* 1977; Friberg *et al.* 1978) have examined the incidence of androgen receptors (AR) in endometrial carcinoma. We wish to report our results of receptor analyses in 155 endometrial carcinomas with special attention to the association of histology, tumour differentiation and myometrial invasion.

Materials and methods

Tumour was obtained from 155 patients at curettage or hysterectomy; a piece of tissue was taken for histology and the remainder stored at −70°C for varying periods up to 1 month. Steroid receptors were analysed as described previously (Quinn *et al.* 1982) and a value of ⩾5 mol/mg protein was considered positive. ER was measured in all 155 tumours, PR in 148 and AR in 118. Six patients did not have a hysterectomy so the association between myometrial invasion and receptor content could be investigated in 149 tumours.

Histological grading was according to FIGO specifications and tumours were classified as adenocarcinomas (grades 1–3), adenosquamous carcinomas (A/Sq) or clear-cell carcinomas (CC).

Statistical analysis was by the χ^2 test and Wilcoxon's two-sample test. Mean values were analysed for receptor-positive tumours only.

Results

Associations with histology

Adenocarcinomas were graded according to differentiation: G_1 for well-differentiated, G_2 for moderately well-differentiated and G_3 for poorly-differentiated tumours.

The presence of ER (ER+) was detected in 120 tumours (77%), PR+ was detected in 108 (73%) and AR+ in 70 (59%). AR+ was significantly less common than ER+ ($\chi^2 = 9{\cdot}53$, $P<0{\cdot}005$) and PR+ ($\chi^2 = 4{\cdot}93$, $P<0{\cdot}05$). The incidence of positive receptors according to histological type and differentiation is depicted in Table 1: ER+ occurred significantly more often in G_1 tumours than in G_2 ($\chi^2 = 4{\cdot}03$, $P<0{\cdot}05$) or in G_3 ($\chi^2 = 39{\cdot}26$, $P<0{\cdot}001$) adenocarcinomas. PR+ was also significantly more likely to be present in G_1 tumours than in G_2 ($\chi^2 = 7{\cdot}65, P<0{\cdot}01$) or in G_3 ($\chi^2 = 12{\cdot}13, P<0{\cdot}001$) tumours. The incidence of AR+ was significantly increased in G_1 tumours compared with G_3 tumours ($\chi^2 = 10{\cdot}15$, $P<0{\cdot}005$) but was similar to that in G_2 tumours. G_1 tumours showed highly significant increased incidences of ER+ ($\chi^2 = 26{\cdot}41, P<0{\cdot}001$), PR+ ($\chi^2 = 14{\cdot}21$, $P<0{\cdot}001$) and AR+ ($\chi^2 = 5{\cdot}98$, $P<0{\cdot}02$) when compared with all the other adenocarcinomas.

Table 1. Incidence of positive receptors according to histology

Receptor	G_1	G_2	G_3	A/Sq	CC
ER+	64/67 (96)	19/24 (79)	11/31 (35)	22/26 (85)	4/7 (57)
PR+	54/62 (87)	13/23 (57)	16/31 (52)	20/25 (80)	5/7 (71)
AR+	36/49 (80)	14/20 (70)	8/25 (32)	10/18 (56)	2/6 (33)

Values in parentheses are percentages.

Table 2. Receptor combination according to histology

Receptors	G_1	G_2	G_3	A/Sq	CC
ER+ PR+	53	11	9	18	4
ER+ PR−	6	8	2	3	0
ER− PR+	1	2	7	2	1
ER− PR−	2	2	13	2	2
ER+ AR+	36	13	6	10	2
ER+ AR−	11	4	0	5	0
ER− AR+	0	1	2	0	0
ER− AR−	2	2	17	3	4

The association of histology with combinations of ER+ and PR+ and with combinations of ER+ and AR+ is shown in Table 2. The combination ER+ PR+ occurred significantly more often in well-differentiated adenocarcinomas than in G_2 carcinomas ($\chi^2 = 10{\cdot}85$, $P<0{\cdot}001$) or in G_3 adenocarcinomas ($\chi^2 = 27{\cdot}15$, $P<0{\cdot}001$) but there was no significant difference in the incidence of ER+ PR+ in G_1 or in G_2 tumours compared with that in adenosquamous tumours. However, the incidence of ER+ PR+ was significantly lower in G_3 tumours ($\chi^2 = 8{\cdot}58$, $P<0{\cdot}005$) than in adenosquamous tumours. Conversely, G_3 tumours were significantly more likely to be ER negative (ER−) combined with PR− than were G_1 ($\chi^2 = 16{\cdot}91$, $P<0{\cdot}001$) or adenosquamous tumours ($\chi^2 = 6{\cdot}49, P<0{\cdot}02$). Furthermore, G_3 tumours were significantly more likely to be ER− PR+ than were G_1 tumours ($\chi^2 = 9{\cdot}04$, $P<0{\cdot}005$) or G_1 and G_2 tumours analysed together ($\chi^2 = 8{\cdot}19, P<0{\cdot}005$).

Well-differentiated tumours were also significantly more likely to be ER+ AR+ than were G_3 tumours ($\chi^2 = 14{\cdot}55$, $P<0{\cdot}001$) whereas G_3 tumours were significantly more likely to be

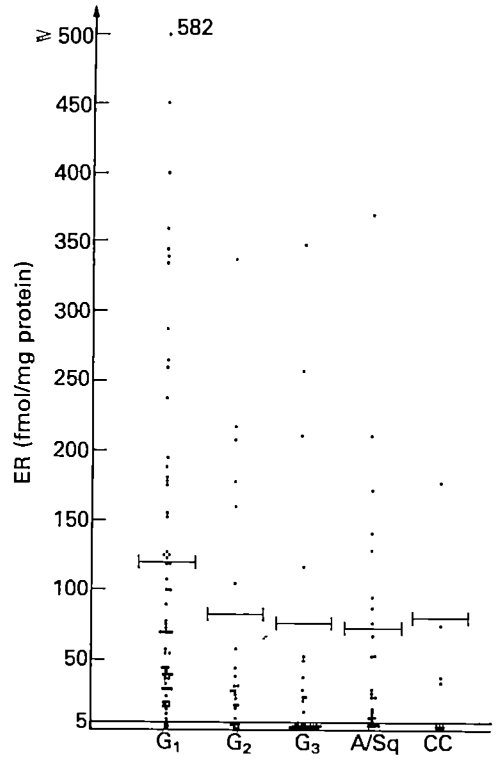

Fig. 1. Oestrogen receptor (ER) values and histology in endometrial carcinomas. (Horizontal bars are mean values of receptor positive samples.) G_1, G_2, G_3, grades 1–3 adenocarcinomas; A/Sq, adenosquamous carinoma; CC, clear-cell carcinoma.

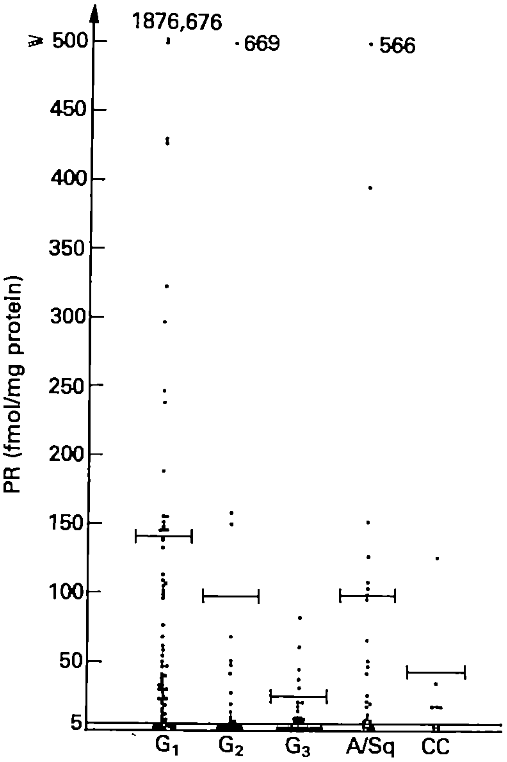

Fig. 2. Progesterone receptor values and histology in endometrial carcinomas. (Horizontal bars are mean values of receptor positive samples.) Abbreviations as in Fig. 1.

ER– AR– than were G_1 ($\chi^2 = 32{\cdot}17$, $P<0{\cdot}001$) or adenosquamous ($\chi^2 = 9{\cdot}12$, $P<0{\cdot}005$) carcinomas.

Figs 1, 2 and 3 depict the scatter of values of ER, PR and AR respectively. The mean ER content in ER+ G_1 tumours was not significantly higher than that in ER+ G_2 or G_3 tumours analysed separately but it was significantly higher ($P<0{\cdot}05$) than that in ER+ G_2 and G_3 tumours analysed together.

The mean PR content in PR+ G_1 tumours was significantly higher than that in PR+ G_3 tumours ($P<0{\cdot}001$) and that in PR+ G_2 and G_3 tumours analysed together ($P<0{\cdot}001$). The AR content was much less than the ER or PR content, and although the mean content of AR in AR+ G_1 tumours was higher than the values found in AR+ G_2 or AR+ G_3 tumours, the differences were not statistically significant.

When adenosquamous and clear cell carcinomas were compared with all adenocarcinomas, there were no significant differences in the incidences of ER+, PR+ and AR+, nor in mean receptor content in receptor-positive tumours, but adenosquamous carcinomas were significantly more likely to be ER+ than were G_3 adenocarcinomas ($\chi^2 = 12{\cdot}06$, $P<0{\cdot}001$).

Associations with myometrial invasion

Invasion was not significantly related to the incidence of ER+, PR+ or AR+ in G_1 and G_2 tumours. Poorly-differentiated tumours, however, were significantly less likely to be ER+ when invasion was greater than two-thirds ($\chi^2 = 9{\cdot}48$, $P<0{\cdot}005$). When all adenocarcinomas were analysed together, tumours invading more than two-thirds of the myometrium were significantly less likely to be ER+ ($\chi^2 = 12{\cdot}19$, $P<0{\cdot}001$), PR+ ($\chi^2 = 14{\cdot}30$, $P<0{\cdot}001$) or AR+ ($\chi^2 = 6{\cdot}19$, $P<0{\cdot}02$).

There was no significant association between invasion and the incidence of positive receptors in adenosquamous or clear-cell carcinomas.

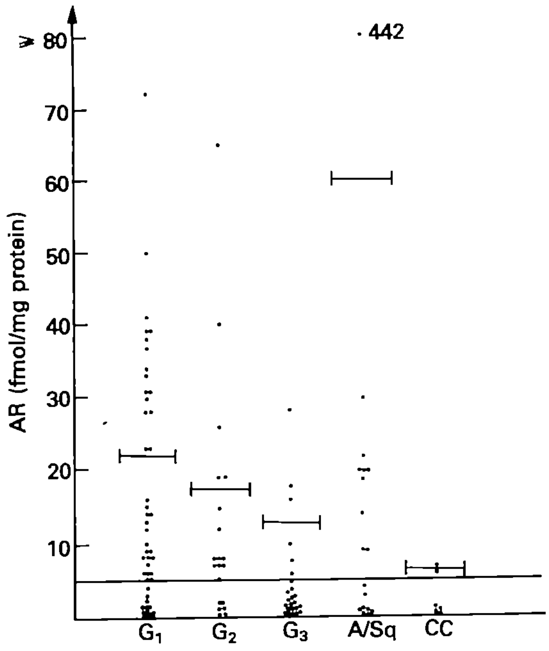

Fig. 3. Androgen receptor values and histology in endometrial carcinomas. (Horizontal bars are mean values of receptor positive samples.) Abbreviations as in Fig. 1.

For all tumours, invasion greater than two-thirds of the myometrium was associated with a significant reduction in the incidences of ER+ ($\chi^2 = 11{\cdot}41, P<0{\cdot}001$), PR+ ($\chi^2 = 13{\cdot}69, P<0{\cdot}001$) or AR+ ($\chi^2 = 5{\cdot}38, P<0{\cdot}05$).

Analysis of receptor combinations in adenocarcinomas which invaded more than two-thirds of the myometrium revealed that the combination ER+ PR+ was significantly less common in G$_1$ tumours ($\chi^2 = 5{\cdot}57$, $P<0{\cdot}02$) or in G$_3$ tumours ($\chi^2 = 3{\cdot}93$, $P<0{\cdot}05$) than in G$_1$ or G$_3$ tumours which invaded two-thirds or less of the myometrium.

Invasion had no significant association with the incidence of ER+ AR+ nor with the incidence of ER− AR− when the adenocarcinomas were analysed separately. But when G$_2$ and G$_3$ tumours were analysed together, invasion greater than two-thirds of the myometrium was associated with a significantly reduced incidence of ER+ AR+ tumours ($\chi^2 = 12{\cdot}31$, $P<0{\cdot}001$) and a significantly increased incidence of ER− AR− tumours ($\chi^2 = 7{\cdot}86$, $P<0{\cdot}01$) when compared with invasion of two-thirds or less.

Figs 4 and 5 depict the association between myometrial invasion and receptor content of ER and PR respectively. Mean ER content in ER+ G$_1$ tumours which invaded less than one-third of the myometrium was significantly higher than that in G$_1$ tumours which invaded more than one-third of the myometrium ($P = 0{\cdot}01$). There was no association between invasion and mean ER content in G$_2$, G$_3$, adenosquamous or clear cell tumours but it should be noted that no G$_3$ tumour invading more than two-thirds of the myometrium was ER+. When all tumours were analysed as a group, the mean ER content was significantly lower in the tumours invading two-thirds or more of the myometrium ($P = 0{\cdot}03$).

The mean PR content in PR+ G$_1$ tumours which were less than one-third invasive was significantly higher than the mean content in PR+ G$_1$ tumours which were more than two-thirds invasive ($P<0{\cdot}05$). No other significant associations were found between invasion and PR content in any of the other PR+ tumour groups. But when all tumours were analysed as a group, the mean PR content in the PR+ tumours was significantly lower ($P<0{\cdot}01$) when invasion was two-thirds or more. There was no significant association between invasion and mean AR content in the AR+ tumours.

Correlations between receptors

Table 3 lists the correlation coefficients and significance values between receptors for all tumours and for individual histological subtypes.

Table 3. Correlations between receptors

	Correlation coefficient r	P
ER versus PR		
G$_1$	0·5277	<0·001
G$_2$	0·511	<0·02
G$_3$	0·7281	<0·001
A/Sq	0·6569	<0·001
All tumours	0·5579	<0·001
ER versus AR		
G$_1$	0·5794	<0·0001
G$_2$	0·3631	NS
G$_3$	0·6062	<0·01
A/Sq	0·8517	<0·001
All tumours	0·4287	<0·001

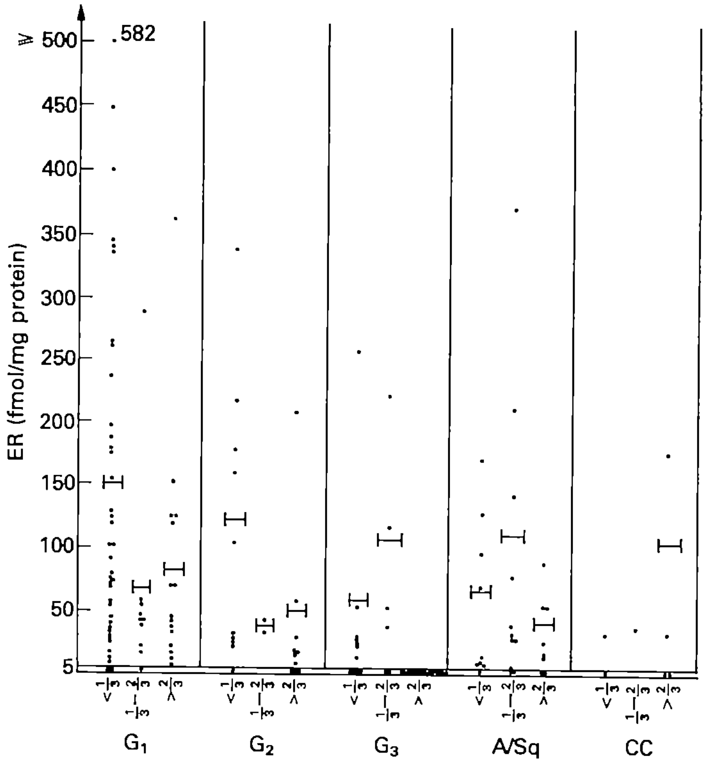

Fig. 4. Oestrogen receptor values, histology, and depth of myometrial invasion in endometrial carcinomas. (Horizontal bars are mean values of receptor-positive samples.) Abbreviations as in Fig. 1.

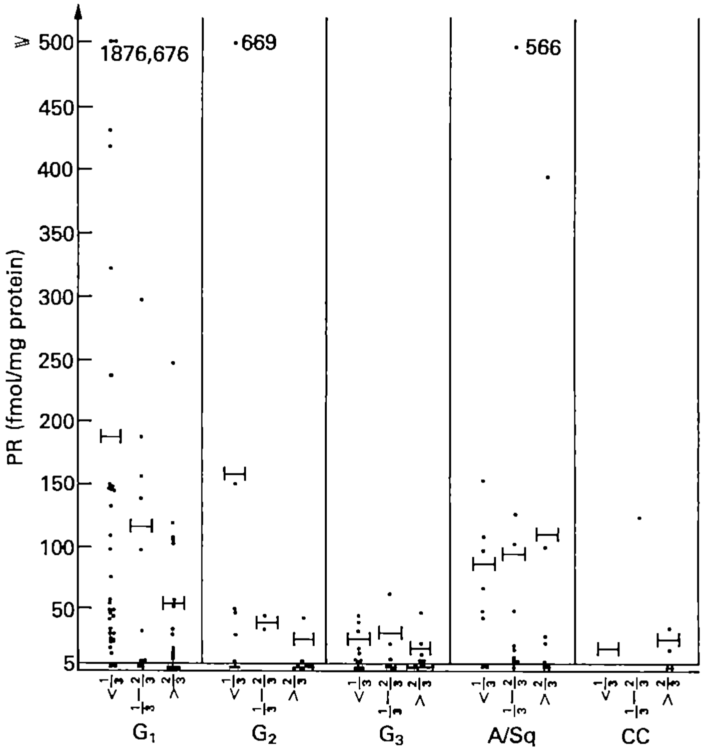

Fig. 5. Progesterone receptor values, histology and depth of myometrial invasion in endometrial carcinomas. (Horizontal bars are mean values of receptor-positive samples.) Abbreviations as in Fig. 1.

There was a highly significant correlation between ER+ and PR+, and ER+ and AR in G_1 and G_3 adenocarcinomas and adenosquamous tumours. When all tumours were analysed together a significant correlation between ER+ and PR+, and ER+ and AR+ was again present.

Discussion

The incidence of ER+ and PR+ adenocarcinomas in our study is similar to that in previous reports (Richardson & MacLaughlin 1983). This is the first report on the incidence of steroid receptors in adenosquamous and clear-cell carcinomas, and, interestingly, these tumours have receptor profiles more closely aligned with well-differentiated adenocarcinomas than with poorly-differentiated adenocarcinomas despite sharing the prognostic significance of the latter. It is impossible to tell whether the receptor content of the adenosquamous carcinomas was related to the glandular or the squamous component of the tumours. That the relatively high incidence and content of receptors may be due to the squamous component is supported by the findings of ER (Martin *et al.* 1982) and PR (Gao *et al.* 1983) in squamous carcinomas of the cervix. The presence of AR in the majority of endometrial tumours has been confirmed in this much larger series of patients, although values tended to be much lower than those of ER and PR.

Tumour differentiation showed a strong association not only with the incidence of ER+, PR+ and AR+, but also with receptor content. Well-differentiated tumours were significantly more likely to be receptor-positive than less well-differentiated tumours which is in keeping with the vast majority of reported series. Furthermore, well-differentiated tumours were significantly more likely to be ER+ PR+, and ER+ AR+ than poorly-differentiated tumours. Our results also show that when ER and PR are present in endometrial adenocarcinomas, receptor levels are higher when the tumour is well-differentiated suggesting that as tumours de-differentiate receptor levels fall and eventually become undetectable.

Since well-differentiated tumours are less likely to be deeply invasive than poorly-differentiated tumours, analysis of the relation of invasion to receptor status must be performed for both histological type as well as for the tumour spectrum as a whole, since a reduced content of receptors in deeply invasive tumours may simply represent an increased incidence of anaplastic tumours in this group. This was taken into account in the study by Creasman *et al.* (1980) but not in the study by Kauppila *et al.* (1982*b*). Thus, in our series, deep myometrial invasion (more than two-thirds) was associated with a significantly reduced incidence of ER, PR and AR when all tumours were analysed together, but this held true only for ER and only in poorly-differentiated tumours when each histological subtype was analysed separately. Nonetheless, well- and poorly-differentiated tumours were both less likely to be ER+ PR+ when invasion was deep, and when moderately well- and poorly-differentiated tumours were analysed as one group, ER+ AR+ tumours were less likely to exist when invasion was deep. It is especially interesting to note that no poorly-differentiated, deeply invasive tumours contained ER (Fig. 4). Likewise, receptor values of ER and PR were significantly lower in well-differentiated tumours once invasion was greater than one-third of the myometrium.

The finding of a tumour that is PR+ or AR+ in combination with ER− could be accounted for by a number of possibilities. (1) Endogenous steroids interfered with the assay as reported by Sarrif & Durant (1981) for breast carcinoma, but this is obviated in our analysis by pretreatment of samples with dextran-coated charcoal. (2) All cytosolic ER were occupied and the assay, which measures only unoccupied sites, was misleading; we have discounted this possibility by performing exchange assays at 25°C (unpublished observations). (3) All cytosolic ER have been translocated to the nucleus; data from Neumannova *et al.* (1983) suggests that this is unlikely. (4) As the tumour becomes more anaplastic, regulation of receptor production is altered; supporting this was the significantly increased incidence of ER− PR+ poorly-differentiated tumours, but against this was the excellent correlation between ER and PR, and between ER and AR in poorly-differentiated tumours which suggests that altered receptor kinetics may occur in a proportion of tumours, and that such altered kinetics may be different for PR and AR production.

By analogy with their use in breast cancer, observations on the incidence of receptors in endometrial cancer are likely to provide the basis for the clinical application of therapy. At this stage, the usefulness of receptor assays in endometrial cancer in this respect has not been fully analysed and meanwhile, collection of basic information must continue, so that the presence or absence of receptors as an independent prognostic guide and as a guide to response to hormonal therapy can be fully assessed.

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A prospective trial of computed tomography in the staging of ovarian malignancy

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Summary. Thirty patients, thought clinically to have ovarian tumours, were studied prospectively by pre-operative computed tomographic (CT) scans of the abdomen and pelvis. In six patients (20%) small metastases in mesentery, omentum and on subdiaphragmatic peritoneum were not detected by the scans. CT did not improve the accuracy of staging or assist the surgeons by drawing their attention to disease which they might otherwise have missed. Although CT gives an elegant demonstration of anatomy, it is not an alternative to extended laparotomy in patients with ovarian tumours.

Ovarian tumours are often silent in their early stages and the disease may be widespread when first detected. Metastases may occur in the peritoneum, omentum, liver, lungs or retroperitoneal lymph nodes. Recent work has suggested that results of treatment are improved if, before chemotherapy or radiotherapy, an extended laparotomy is performed to allow 'debulking' of abdominal tumour masses together with hysterectomy and bilateral salpingo-oophorectomy (Dembo *et al.* 1979; Bush 1979). Such an approach requires a long vertical incision for the initial laparotomy with consequent potential morbidity. If pre-operative assessment by computed tomography (CT) could accurately separate patients with disease confined to the pelvis from those with extrapelvic metastases, then it may be possible to limit the extent of surgery in the former. Previous studies of CT in ovarian cancer have been largely retrospective and no clear role has emerged (Mamtora & Isherwood 1982; Solomon *et al.* 1983).

In 1981 we began a prospective study to determine whether prelaparotomy CT scanning could demonstrate the full extent of disease, so assisting surgery in women thought clinically to have ovarian cancer.

Patients and methods

Thirty-two women aged 36–81 years had CT scans between December 1981 and November 1983. Two patients were unfit for laparotomy and so were withdrawn from the study leaving 30 patients for analysis (Table 1).

CT scans

CT scans (Philips Tomoscan 300) were performed 30 min after patients were given 800 ml of 4% Gastrografin orally. Intravenous contrast media were not used routinely. Sections of 12 mm thickness were obtained from symphysis pubis to carina, contiguous slices in the pelvis, and only alternate slices in the upper abdomen and lungs. All the CT scans were assessed by one

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Table 1. Comparison of computed tomography (CT) and surgical staging

CT staging	Surgical staging I or benign	II	III	IV	Total
I or benign	13	1*	1	—	15
II	3†	2	2**	—	7
III	1*	—	4	—	5
IV	1‡	—	—	2	3
Total	18	3	7	2	30

* Benign histology

** Includes one patient with benign histology.

† Includes one patient with carcinoma of a fallopian tube.

‡ Benign ovarian cyst and liver haemangioma

radiologist; his sealed reports were available to the surgeons at laparotomy but were not read until the staging process had been completed.

Operation was usually undertaken within a few days of the CT scan. The abdomen was opened through a vertical lower abdominal incision, extended when appropriate to expose the entire peritoneal cavity. Peritoneal fluid or washings or both were sent for cytological examination. The omentum, bowel, liver, inferior surface of the diaphragm and lymph nodes were examined and in some cases biopsied. The CT scan report was then read and if features were recorded which had not been observed during the initial procedure, further exploration was peformed immediately. Surgical treatment was decided on the basis of the operative findings Most patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and, where indicated, additional procedures such as omentectomy; if the lesion was thought to be benign more limited surgery was undertaken. After each operation the surgeon recorded his initial findings and whether the CT report had provided new information which had altered his assessment of the patient's disease.

Results

Discrimination between ovarian and other abnormalities

The CT scan indicated ovarian disease in 28 patients. At laparotomy this was confirmed in 27; two of the other patients had only uterine disease and one (Fig. 1) had fibroids and endometriosis. Histological examination in the last-named patient also showed a small carcinoma of the fallopian tube.

Discrimination between benign and malignant disease

Initially, CT assessment of staging was based on the presumption of malignancy, so stage I and benign lesions are grouped together in Table 1.

Lesions were regarded as malignant if CT showed solid components in an ovarian tumour, direct invasion of adjacent organs or metastases (Rohde & Steinbrich 1983). Three patients were considered on CT to have benign disease, one with simple ovarian cyst and two with uterine fibroids; all these were confirmed as benign by surgery and histology. Of the 27 assessed as malignant by CT, 10 appeared benign at surgery and none of these showed histological evidence of malignancy. One of these patients had a benign liver tumour (Fig 2) whilst in the other nine difficulty in defining the local extent of the primary lesion made it impossible to distinguish between benign and stage I lesions. Three of the 17 lesions interpreted as malignant by both CT and surgery had benign histology.

Staging

Table 1 shows the results of staging by CT and by surgery. CT suggested that in 22 patients disease was confined to the pelvis (i.e. was stage I or II) but laparotomy showed that in three of these patients disease had spread into the upper peritoneal cavity. Histologically, however, one of these three had benign disease (benign ovarian cyst and omental fat necrosis—Fig. 3).

Both CT and laparotomy assessed four patients to be stage III. One other patient was assessed as stage III on CT but both surgical inspection and histology showed only benign

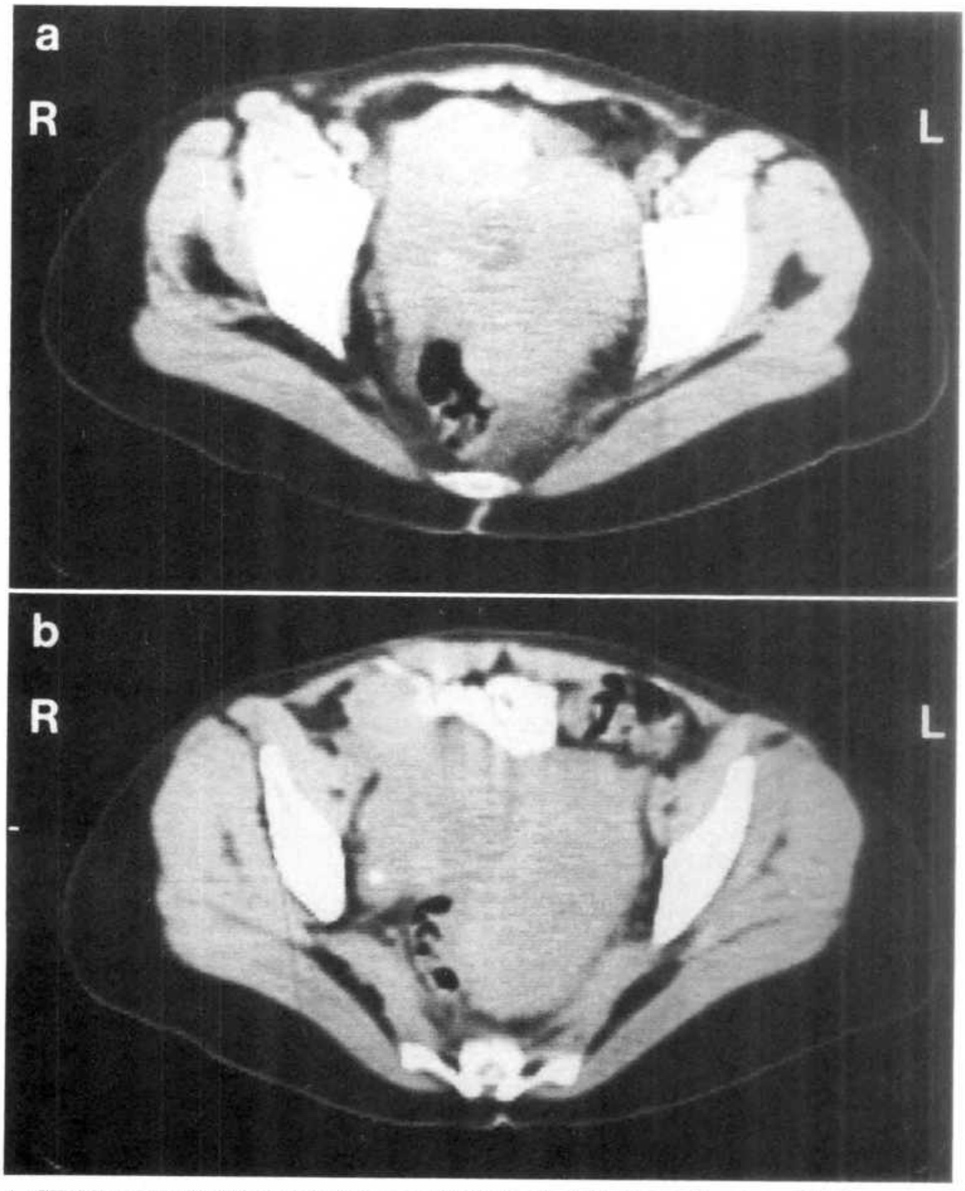

Fig. 1. CT shows a lobulated mixed density mass with flecks of calcification in the uterus. CT diagnosis: ovarian carcinoma stage IIA, fibroid uterus; laparotomy diagnosis: fibroids; histology: fibroid uterus, endometriosis, carcinoma of fallopian tube.

disease; adhesions may have caused the CT appearance. CT did not detect deposits on the subdiaphragmatic peritoneum of one patient or involvement of the sigmoid colon and omentum in another but their staging was not affected.

CT assessed three patients to be stage IV. One had lung lesions and in a second patient CT detected a pleural effusion but missed omental and subdiaphragmatic disease; pleural and omental metastases were confirmed histologically. In a third patient CT showed bilateral ovarian lesions and a mass in the liver; histology revealed benign ovarian cysts and a hepatic haemangioma.

Staging by CT and surgery agreed in 21 of 30 patients which is significantly different from what would be expected by chance alone ($P < 0{\cdot}01$ using standard normal deviate test). Of the nine discrepant results, surgical findings were confirmed by histology in seven.

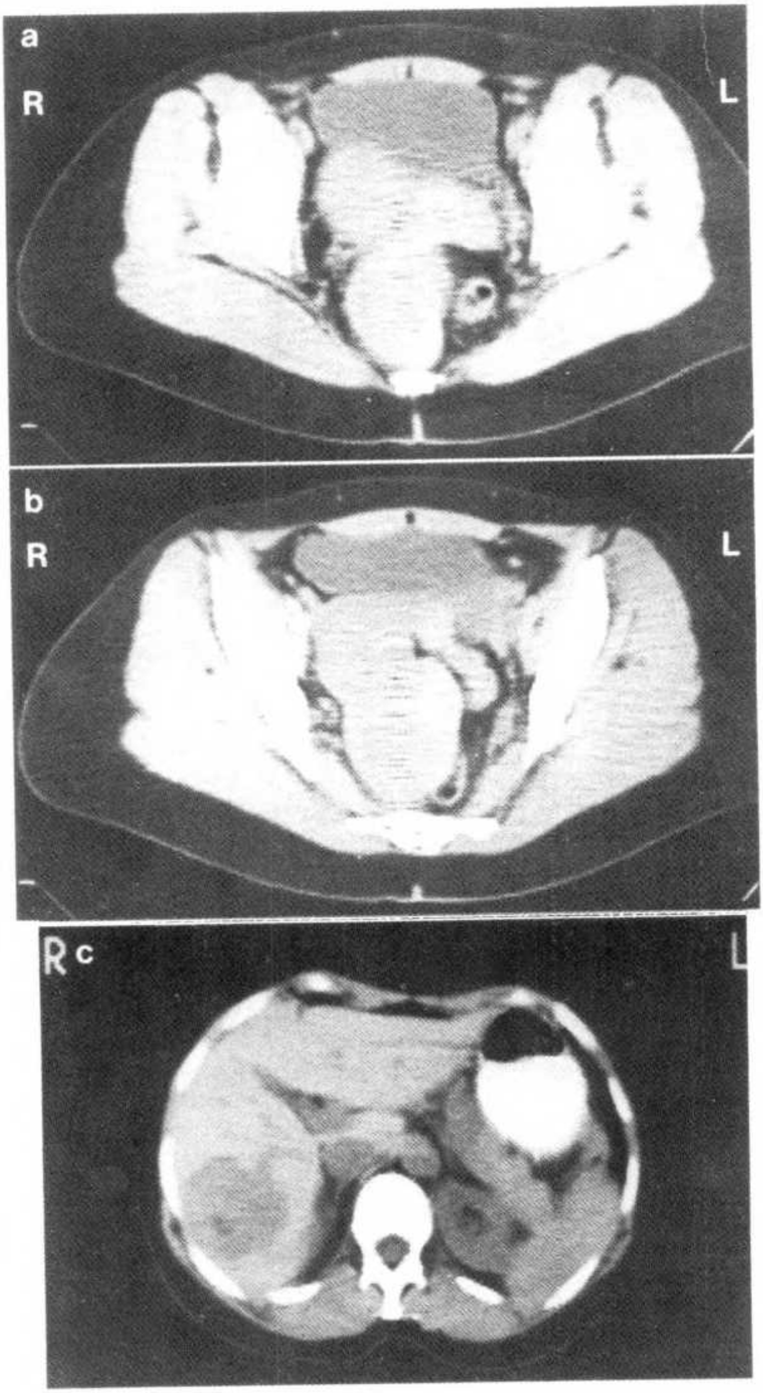

Fig. 2. A bilobed mass of mixed density arises in the pelvis; the liver contains a mass of tumour density. CT diagnosis: ovarian carcinoma stage IV; laparotomy diagnosis: endometriotic cysts, normal liver; histology: benign ovarian cysts, haemangioma of the liver.

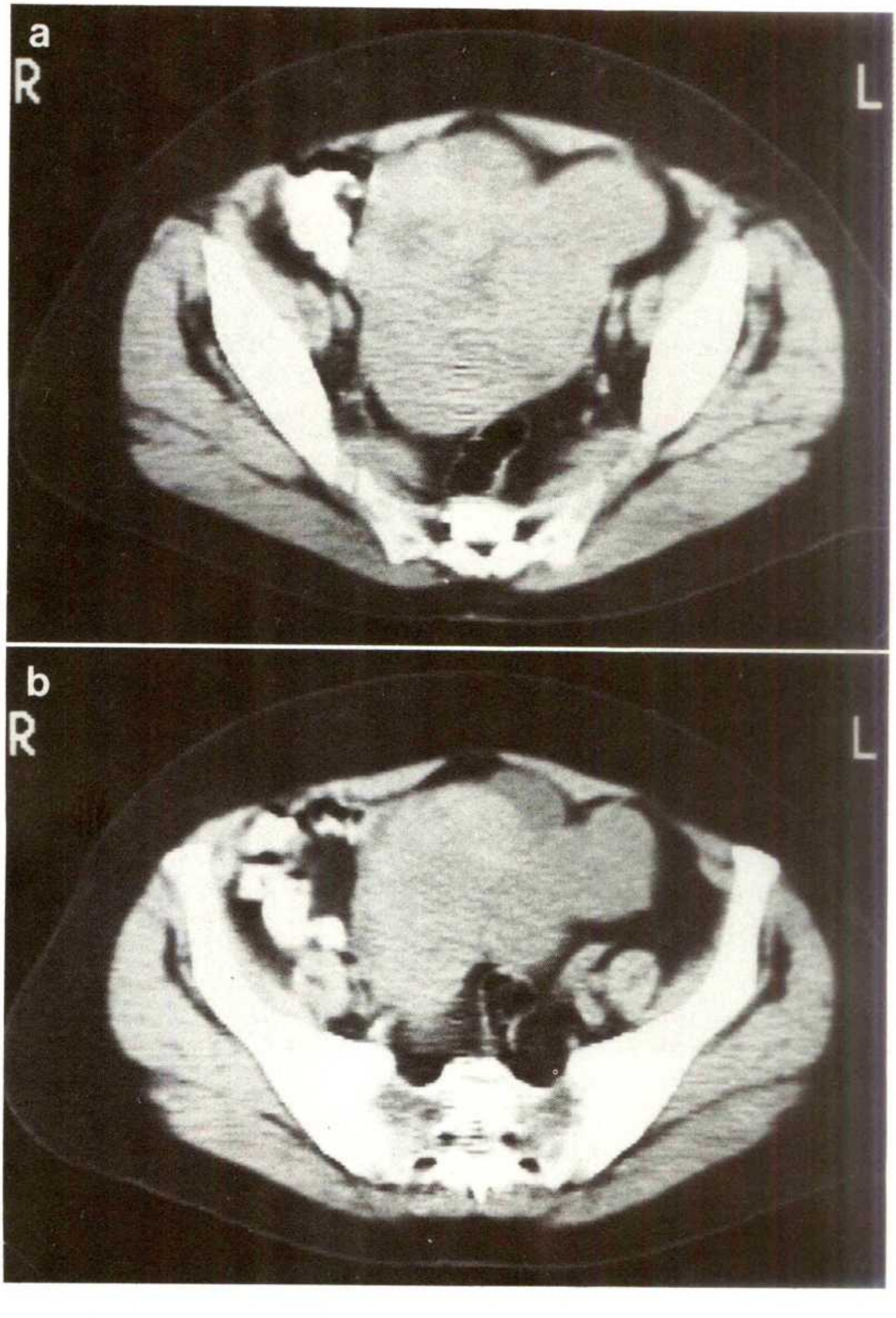

Fig. 3. A lobulated mass of mixed but largely solid density arises in the pelvis. CT diagnosis: ovarian carcinoma stage II; laparotomy diagnosis: ovarian carcinoma stage III; histology: benign ovarian fibroma with a simple serous cyst and omental fat necrosis.

Discussion

The finite slice thickness inherent in CT results in the edges of curved structures being blurred because of volume averaging. This is a particular problem in the pelvis where the bladder, small bowel, colon, uterus and ovaries may all present curved surfaces within the same slice.

Difficulties are increased with previous surgery, pelvic inflammatory disease or endometriosis. As would be expected, surgical opinion formed at laparotomy was more often correct than CT assessment in deciding whether a lesion was benign or malignant. CT detected solid areas within cysts and often identified adhesions and distant lesions; all of these were taken to indicate malignancy, but adhesions may be benign and distant lesions may be unrelated. The false-positive CT interpretations resulted from coincident benign disease in five patients, either focal or distant; the other five were the result of the inability of CT to distinguish between benign cysts and stage I disease. Illustrations of these difficulties are given in Figs 1–3.

CT does help to demonstrate the size of ovarian and other pelvic tumours and the extent of spread in omentum, bowel, nodes, liver and lungs but small peritoneal metastases may be beyond the limits of resolution (Amendola *et al.* 1981; Mamtora & Isherwood 1982, Solomon *et al.* 1983; Johnson *et al.* 1983). In our series the smallest peritoneal deposits detected were about 2 cm in diameter; CT missed lesions in the mesentery of one patient, on the subdiaphragmatic peritoneum of two and in the omentum of four. No currently available, non-invasive, investigative technique can detect small peritoneal, omental or mesenteric deposits (Levitt *et al.* 1978; Whitley *et al.* 1981). The role of CT in the detection of residual and recurrent disease after primary treatment remains to be fully assessed (Stern *et al.* 1981; Walsh *et al.* 1978).

In our series, CT did not identify disease which the surgeons might otherwise have missed, and we conclude that pre-operative CT cannot replace extended laparotomy in staging ovarian cancer.

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Recurrent pregnancy-induced thyrotoxicosis presenting as hyperemesis gravidarum. Case report

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Case report

The patient was a Pakistani woman who had hyperemesis gravidarum in each of her first two pregnancies and was found to be biochemically thyrotoxic on each occasion. She was 26 when she presented with vomiting, lassitude and weight loss during the 9th week of her first pregnancy. Her weight on admission to hospital was 38·4 kg and fell to 33·7 kg over the succeeding 7 weeks despite intensive support.

She was withdrawn, wasted and apathetic. She had a tachycardia (despite rehydration) with a sleeping pulse rate of 110–120 beats/min. There were no specific clinical signs of thyroid disease.

Her thyroid function test results are summarized in Table 1 and confirm the diagnosis of thyrotoxicosis. An intravenous 200 μg TRH test showed no response of immunoreactive TSH with levels of 5·2, 6·2 and 6·1 mU/l at 0, 20 and 60 min. Thyroid cytoplasmic and thyroglobulin antibodies were negative, as were LATS and LATSP (kindly assayed by Professor D. S. Munro). Plasma and urinary hCG levels lay within the reference range. There was no evidence of trophoblastic disease and the pregnancy was single.

Treatment with carbimazole (10 mg twice daily) was commenced at 15 weeks and was accompanied by prompt improvement in her sickness and malaise. She was discharged home 17 days later. The dose of carbimazole was reduced to 5 mg daily and her subsequent course until the birth of a healthy baby at term was uneventful. The drug was discontinued altogether after delivery. There was no evidence of intrauterine or neonatal thyroid disease.

The patient remained clinically and biochemically euthyroid until she conceived for a second time. In February 1983 she presented at 11 weeks of pregnancy, again with hyperemesis. Her thyroid function tests are summarized in Table 1 and the TSH levels after TRH (at 13 weeks) were 2·4, 1·6 and 1·6 mU/1 (0, 20 and 60 min). LATS and LATSP levels were negative. The urinary hCG level was elevated above the reference range at 512 000 iu/l at 13 weeks but subsequently fell to normal. Treatment with carbimazole, 5 mg three times daily, was started at 13 weeks and was followed by a marked clinical improvement. She went home after 48 h, and remained well thereafter. Because it was suspected that her condition was hCG-related, carbimazole was discontinued electively at 16-

Table 1. Thyroid hormone levels before treatment in the first and second pregnancies

	T3 uptake	Free T3 index	Free T4 index	Free T4 (pmol/l)
First pregnancy				
10.8.81	102	4·5	313	27
14 8.81	112	4·6	>290	—
Second pregnancy				
26 1.83	95	3·7	311	32
8.2 83	109	4·6	>275	45
12.2.83	111	3·2	>270	49
Normal (non-pregnancy) range	95–118	1·7–2·7	70–125	10–26

weeks. When her TRH test was repeated at 21 weeks, the TSH response was normal (1·0, 10·4, 1·6 mU/l at 0, 20 and 60 min). Both mother and baby remained clinically and biochemically euthyroid throughout the remaining pregnancy, delivery and the puerperium (Fig. 1).

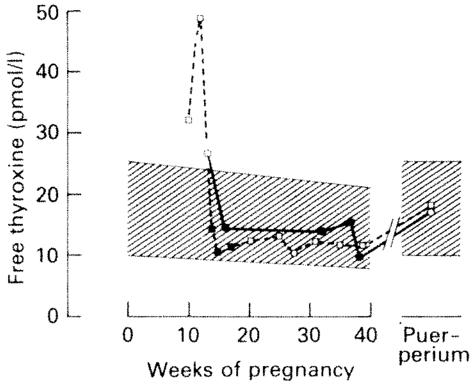

Fig. 1. Free thyroxine levels in the first (circles) and second (squares) pregnancies; filled symbols, on carbimazole; open symbols, off carbimazole.

Discussion

Hyperemesis gravidarum is becoming increasingly rare in Western countries, but sporadic cases occur with an incidence of approximately 0·1% total births (Fairweather 1978). No single explanation of true hyperemesis has been described. Racial, social and nutritional factors have been invoked as causes, and most obstetricians believe that psychological upset plays a major role (Fairweather 1978). However, there have been recent reports of hyperemesis gravidarum being associated with occult thyrotoxicosis (Bruun & Kristofferson 1978; Valentine *et al.* 1980; Bouillon *et al.* 1982). Since vomiting may be a feature of untreated thyrotoxicosis (Rosenthal *et al.* 1976), the association between occult thyrotoxicosis and hyperemesis may be more than just chance.

Occult thyrotoxicosis is also a well-recognized feature of trophoblastic tumours (Higgins *et al.* 1975; Norman *et al.* 1981) and vomiting is a presenting symptom in 14% (Higgins & Hershman 1978) to 26% (Berkowitz & Goldstein 1981) patients with hydatidiform mole. The thyrotoxicosis of trophoblastic tumour may be clinically overt (Berkowitz & Goldstein 1981; Tisne *et al.* 1955; Soutter *et al.* 1981), but it is commonly occult (Norman *et al.* 1981; Nagataki *et al.* 1977). In patients with trophoblastic tumour it is thought that the thyroid stimulation is caused by hCG itself (Nisula *et al.* 1974; Kenimer *et al.* 1975), and not placental thyrotrophin (Cave & Dunn 1976; Morley *et al.* 1976). It is therefore suggested that in hyperemesis gravidarum a similar mechanism may apply, with the vomiting being caused by occult thyrotoxicosis and the thyrotoxicosis itself being caused by the effect of placental hCG on the thyroid. Levels of hCG have been noted to be higher in patients with hyperemesis gravidarum (Brindeau *et al.* 1937; Kauppila *et al.* 1979), although this has not been an invariable finding (Fairweather 1978).

This woman had unequivocal thyrotoxicosis in each of her two pregnancies, but had no evidence of Graves' disease and was normal when not pregnant. During the first pregnancy treatment with carbimazole was continued until term, but in the second it was stopped at 16 weeks. Since her thyrotoxicosis did not recur when the carbimazole was then withdrawn, it was concluded that her thyrotoxicosis may indeed have been caused by hCG or some other placental factor with thyroid-stimulating activity. It was noted that her urinary hCG levels were high at the time of her second presentation.

This case further supports the suggestion that hyperemesis results from occult thyrotoxicosis. In both pregnancies her vomiting stopped and her general condition improved once carbimazole was started. In the first pregnancy carbimazole was started at 15 weeks, and it is possible that the improvement resulted not from the drug but from spontaneous remission. Such remission would be expected as hCG levels fall, and has been documented in untreated hyperemesis gravidarum by Bruun & Kristoffersen (1978). However, the prompt improvement in her second pregnancy occurred at 13 weeks and suggested that it was related to the antithyroid treatment given.

It is concluded that some women with true hyperemesis gravidarum may have occult thyrotoxicosis, and that this may result from stimulation of the thyroid by hCG. It is also concluded that the occult thyrotoxicosis may cause the gastrointestinal upset, and that treatment with carbimazole should be considered, especially if the diagnosis of true hyperemesis gravidarum is made early.

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Paget's disease of the vulva complicated by bladder carcinoma. Case report

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Case report

The patient had had two normal pregnancies, no previous medical or relevant family history, and an uncomplicated menopause at the age of 48. In 1961, age 50, she underwent simple vulvectomy for chronic pruritus, with a histological diagnosis of leukoplakia vulvae. Five years later, with her symptoms unabated and two biopsies in the interim confirming the initial diagnosis, she had a radical vulvectomy including excision of internal and external iliac lymph glands. On this occasion the histological examination found a striking degree of Paget's disease with hyperkeratosis and acanthosis of the stratified squamous epithelium, together with numerous clear Paget cells extending throughout the skin.

In 1968 a cystocoele and rectocoele were repaired, together with vaginal hysterectomy and biopsies of skin from the perianal area and anterior to the urethra. The histological report on the skin biopsies and the vaginal skin excised with the posterior colporrhaphy once more showed extensive Paget's disease, although the uterus and cervix were unremarkable. Further skin excised in 1969 and 1978 from the anterior vulval area and natal cleft again showed typical histological features of Paget's disease. Intense pruritus with redness and thickenning of the skin from the groins through to the buttocks continued during these years, with various episodes of erysipelas and candidal infection being treated appropriately. Four courses of local cryotherapy each achieved only short-term relief of symptoms. From mid-1982 onwards the patient also suffered intermittently from dysuria and frequency of micturition, and various urinary infections were treated. By November 1983 diurnal frequency of micturition had become distressing, and an intravenous urogram showed gross bilateral obstructive uropathy with a pelvic mass encroaching on the bladder. Intense vulval pain made clinical pelvic examination inappropriate.

Examination under general anaesthesia revealed a solid pelvic tumour from the perineum occupying the middle and right side of the pelvis, and cystoscopy showed extensive bladder cancer considered to be inoperable. Biopsies from the bladder lesion showed squamous carcinoma arising from the surface, highly suggestive of primary bladder origin (Fig. 1). A simultaneous vulval biopsy showed Paget's disease with no evidence of tumour within the dermis (Fig. 2). The Paget cells in the vulva were of 'signet ring' appearance, with the nucleus pushed to one side by intracytoplasmic mucin, unlike the cells of the bladder tumour, which showed squamous differentiation suggesting a different cell type. Continuous bladder drainage and analgesia provided symptomatic palliation, but the patient developed progressive renal failure from which she died 3 months later.

Discussion

Since the first description by Paget (1874) of a chronic eczema-like lesion of the areola which culminated in breast cancer, and the first report by Dubreuilh (1901) of Paget's disease affecting the vulva, controversy has continued over the exact pathogenesis of this disease and its variable association with carcinoma.

Paget's disease of the vulva is a relatively uncommon condition. For example, 19 cases were seen for 1000 cases of carcinoma of the vulva between 1932 and 1973 at the Norwegian Radium Hospital (Taylor *et al.* 1975). The condition tends to be multicentric in origin and local recurrence is therefore common, although Paget's cells are not inherently malignant. Distressing pruritus may continue for many years. Hart & Millman (1977), reviewing the published literature, found a 19% incidence of carcinoma of

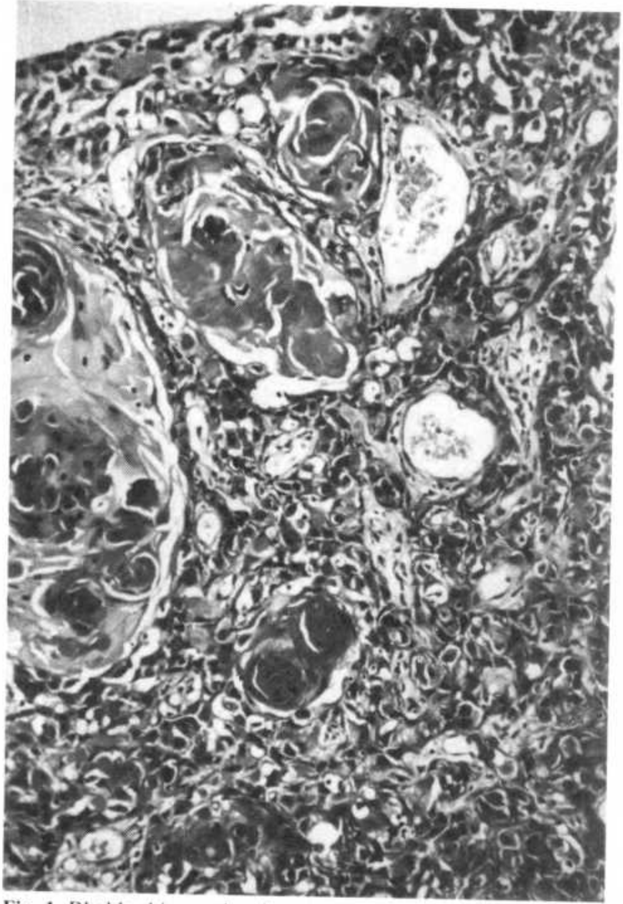

Fig. 1. Bladder biopsy showing squamous carcinoma. ×200.

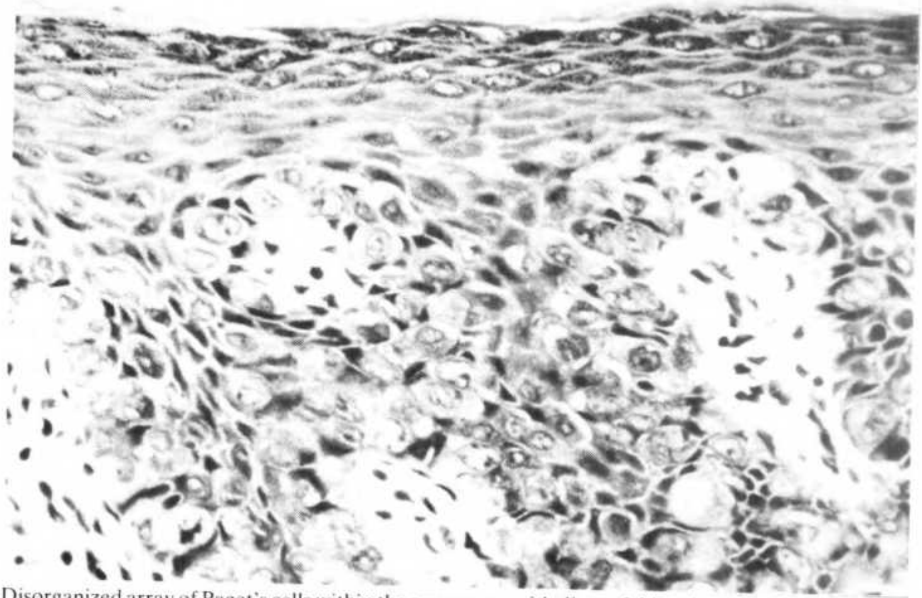

Fig. 2. Disorganized array of Paget's cells within the squamous epithelium of this vulval biopsy, especially along the base. ×520.

the vulva and a 29% incidence of other primary cancers in association with Paget's disease of the vulva. Most cancers associated with extramammary Paget's disease are adenocarcinomas, but two reports have described vulval Paget's disease with squamous cell carcinoma of the cervix (Milne *et al.* 1966) and Paget's disease of the bladder (Lee & Dahlin 1981).

The tragic case reported here illustrates the necessity of continuing vigilance for the appearance of other cancers, even when careful surveillance fails to reveal the development of vulval carcinoma in association with Paget's disease of the vulva. Multifocal epithelial unrest has resulted in recurrent abnormality over many years despite extensive surgical excision. The difficulty of recognizing symptoms possibly indicative of a bladder tumour in the presence of long-standing pain and pruritus in the vulval area is also demonstrated.

Acknowledgments

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Complete psammomatous degeneration of the ovary. Case report

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Case report

A 72-year-old diabetic, nulligravid woman, menopausal since age 52, was sent to our outpatients clinic from the department of endocrinology in March 1982 because of a lower abdominal mass detected at routine examination. Abdominally, a pelvic mass reaching the umbilicus could be palpated, which on vaginal examination seemed to arise from the uterus. Ultrasonography was inconclusive due to the extreme echogenic nature of the mass, suggestive of a large, calcified myoma.

An exploratory laparotomy was performed, revealing a large, stone-hard, multilobulated left ovarian mass (Fig. 1), which was excised. A complete staging laparotomy as for ovarian carcinoma followed, including peritoneal washings and a hysterectomy with right salpingo-oophorectomy. The postoperative course was uneventful.

Pathological findings

The specimen identified as 'left ovary' was a mass measuring 23 × 18 × 13 cm, of firm consistency, with a smooth, unruptured outer surface. Its inner surface (Fig. 2) consisted of finely granulated, calcified nodules, separated by whitish, apparently fibrous tracts. On microscopic examination, a sparse fibrous stroma, surrounding large calcified areas composed of an accumulation of psammoma bodies was seen (Figs 3 and 4). Occasional nests of epithelial cells, suggesting glandular formations in association with psammoma bodies were also observed (Fig. 4).

The right ovary showed on its surface some areas of epithelial invagination related to the presence of psammoma bodies (Fig. 5) but was otherwise normal. The uterus had atrophic endometrium; the fallopian tubes were normal, and the abdominal washings were negative for

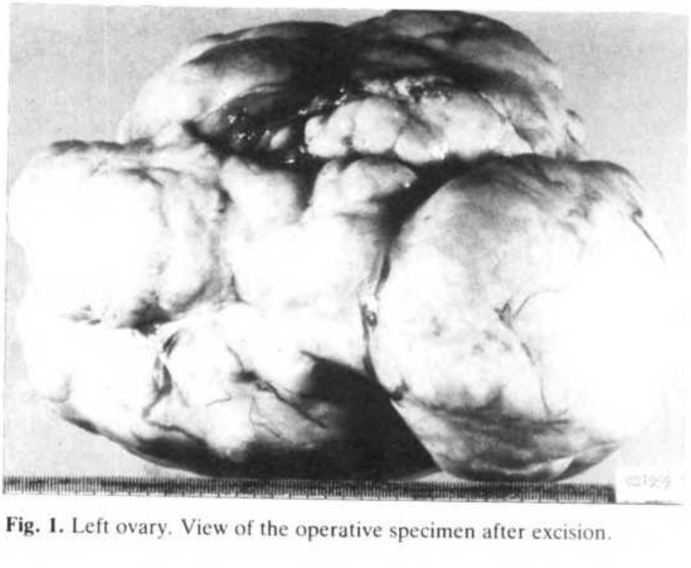

Fig. 1. Left ovary. View of the operative specimen after excision.

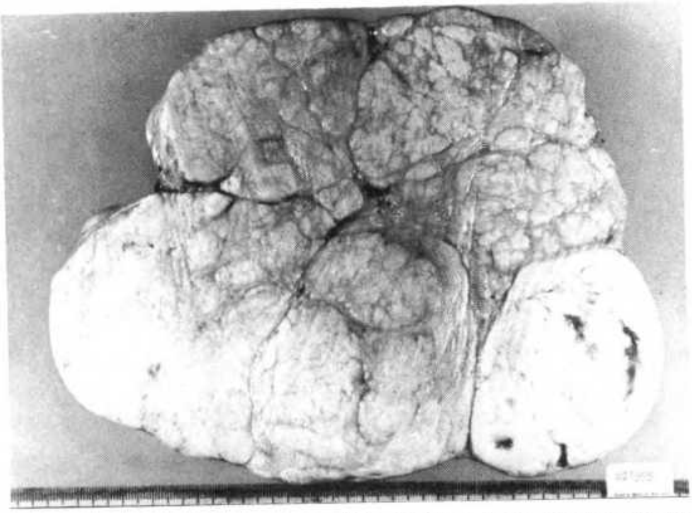

Fig. 2. Section through the specimen of Fig. 1. The uniform, stony consistency of the tumour can be appreciated.

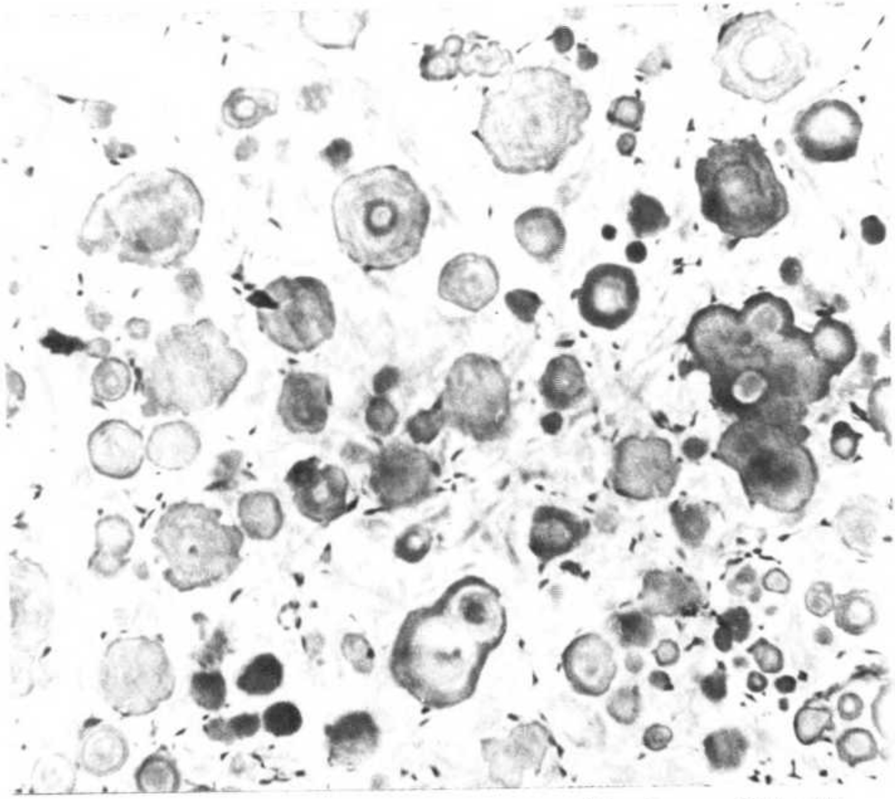

Fig. 3. Accumulation of psammoma bodies with sparse cellular elements. H&E ×100.

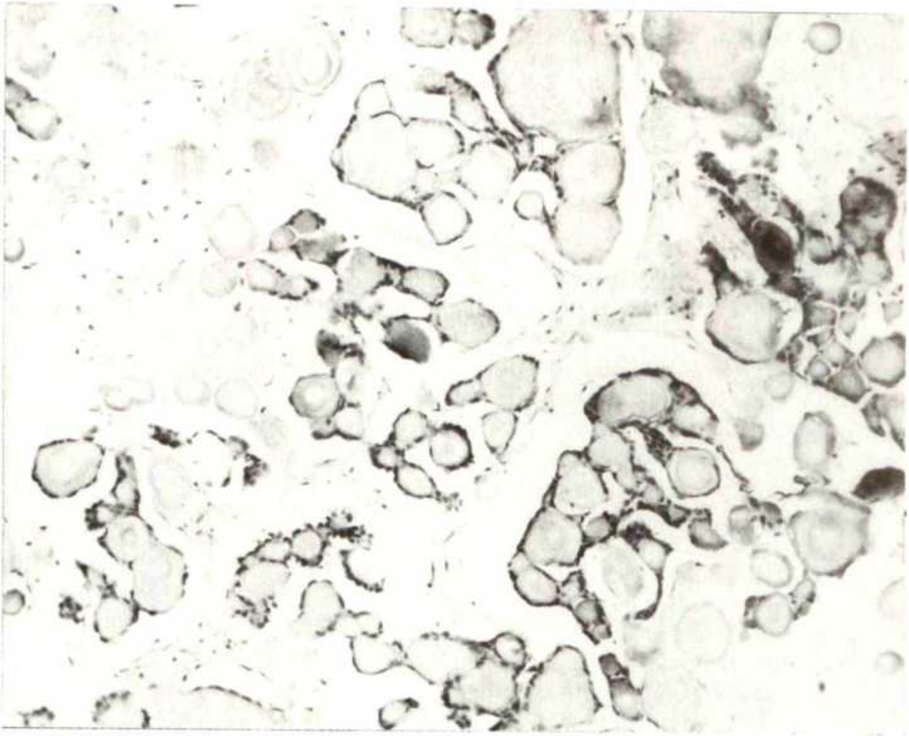

Fig. 4. Clusters of epithelial cells, partly surrounding psammoma bodies. H&E ×100.

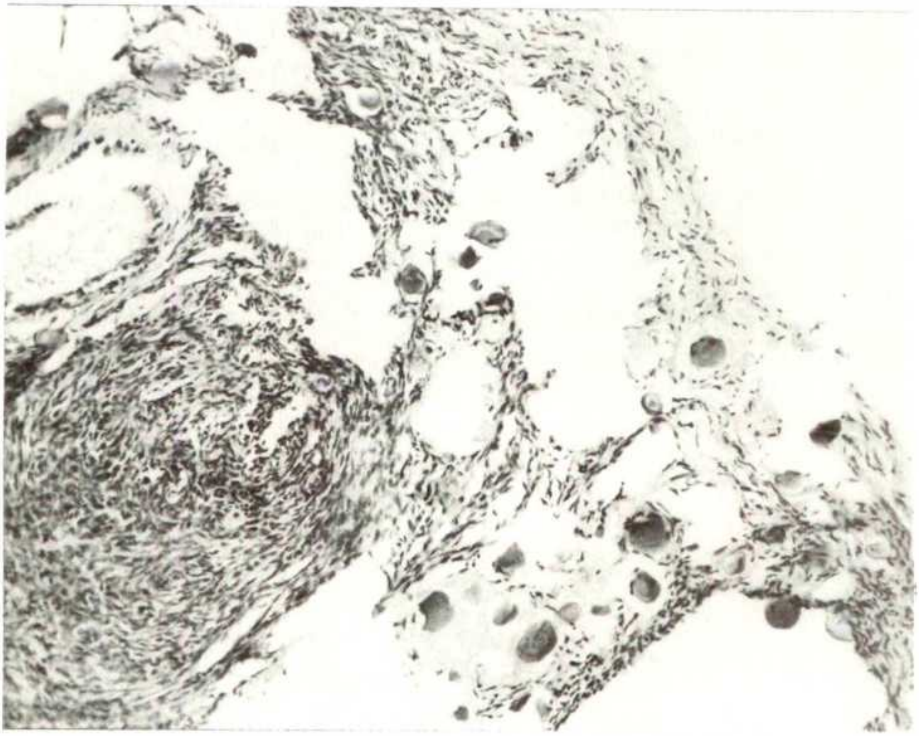

Fig. 5. Right ovary. Psammoma bodies on the periphery. H&E ×40.

malignant cells or psammoma bodies. The diagnosis was a massive psammomatous degeneration of the left ovary of uncertain origin.

Discussion

Psammoma bodies are occasionally found in association with malignant tumours, notably carcinoma of the thyroid and serous cystadenocarcinoma of the ovary (Aure *et al.* 1971; Novak & Woodruff 1979). They have also been found in association with mesotheliomas of the peritoneum and pleura (Rosenthal 1978), as well as in normal tissues, such as the pineal gland, choroid plexuses, meninges and the thyroid gland (Scully 1978), and also near the surface of otherwise normal ovaries, in the absence of any neoplasia (Aure *et al.* 1971). The aetiology of psammoma body formation in the ovary is obscure.

Some authors (Serov *et al.* 1973) consider that they represent evidence of tissue resistance to tumour growth, since they are more commonly seen in low-grade serous tumours, and the term 'psammocarcinoma' has even been coined for the most extreme form of this phenomenon (Shapiro & Nunez 1983). In favour of this theory is the fact that foreign material, such as talc, is occasionally found in the psammoma bodies, suggesting that it acts as an irritant that initiates the atypical proliferation (Aure *et al.* 1971).

Peritoneal mesotheliomas, which often contain psammona bodies, can involve the ovaries secondarily (Novak & Woodruff 1979). This is unlikely to be the case with our patient, since no other tumour could be seen on laparotomy, and the abdominal washings were negative. Since in our patient no foreign material was found in the psammoma bodies, two possible aetiologies remain: either self-destruction by psammomatous degeneration of a borderline serous cystadenocarcinoma, or spontaneous formation of psammoma bodies in a healthy ovary, ultimately involving the whole organ. In favour of the latter possibility is the occurrence of peripheral psammoma body formation in the contralateral ovary.

The patient is alive and well, clinically free of pelvic disease, 2 years after surgery.

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Inappropriate antidiuretic hormone secretion associated with adenocarcinoma of endometrium. Case report

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Case report

A 38-year-old Chinese woman, gravida 3, para 3, was admitted to the Gynaecology Department of Queen Elizabeth Hospital on 26 November 1982 because of menorrhagia. She gave a history of irregular heavy periods for the previous 3 months. Her past health was good. There was no history of drug therapy. She did not experience any excessive thirst or polydipsia. Physical examination revealed mild facial pigmentation. There was no pallor and no ankle oedema. Blood pressure was 110/60 mmHg, pulse rate 100 beats/min. Examination of the heart and chest revealed no abnormality On pelvic examination, clots were removed from the vagina, the uterus was normal size and the fornices were clear. Emergency dilatation and curettage of the uterus was performed. Pathological examination of uterine curettings revealed well-differentiated adenocarcinoma of endometrium.

She was admitted again on 4 December 1982 for total hysterectomy and bilateral salpingo-oophorectomy. Laboratory findings were as follows: haemoglobin 12·4 g/dl, white blood count $5{\cdot}2\times10^9$/l with normal differential, serum sodium 119 mmol/l, potassium 4·6 mmol/l, random plasma glucose 5 mmol/l. Serum osmolality was 245 mosmol/kg with a simultaneous urine osmolality of 758 mosmol/kg.The 24-h urine sodium level was 112 mmol/l. Blood urea nitrogen (BUN) level was 2·1 mmol/l and serum creatinine level 88 μmol/l. Serum T4 and T3, serum SGOT, protein and bilirubin levels were within normal limits. Plasma cortisol levels at 08.00 hours and 22.00 hours were within normal limits. X-ray of skull and chest revealed no abnormality.

Diagnosis of inappropriate antidiuretic hormone (ADH) secretion was made. The hyponatraemia was partially corrected by fluid restriction. Repeat estimations of electrolytes on 7 December 1982 showed: serum sodium 123 mmol/l, potassium 4·7 mmol/l.

Laparotomy with total hysterectomy and bilateral salpingo-oophorectomy was performed on 8 December 1982. At operation, the uterus was found to be bulky in size, the right ovary was enlarged with solid nodular areas containing yellowish viscous material. The left ovary and fallopian tubes were normal. The omentum and liver were normal. No pelvic, iliac or para-aortic adenopathy was felt.

Pathological examinations revealed well differentiated adenocarcinoma of endometrium with metastasis to the right ovary. Microscopic examinations showed endometrial glands with anaplastic change, the cells containing pleomorphic vesicular nuclei with prominent nucleoli. There was a loss of polarity and increased nucleus/cytoplasmic ratio. Aggregates of these tumour tissues were also seen among the myometrium, inside the blood vessels and lymphatics. Metastatic adenocarcinoma was evident in the right ovary. The left ovary and tubes were normal.

The patient made a good recovery from the operation. On the third postoperative day, serum sodium was 136 mmol/l, potassium 4 mmol/l. Serum osmolality was 290 mosmol/kg with simultaneous urine osmolality 348 mosmol/kg She was discharged on the tenth day.

The patient received a course of pelvic irradiation. She was regularly followed up and remained well. The electrolytes, serum osmolality and urine osmolality have remained at a normal level since operation.

Discussion

The syndrome of inappropriate ADH secretion

(SIADH) was not clearly described until 1957 (Schwartz *et al.* 1957). It was more fully characterized by Bartter & Schwartz (1967), and it is now well known that inappropriate ADH secretion may be associated with a host of disease processes, including CNS disorders (meningitis, head injuries, encephalitis, subarachnoid haemorrhage), pulmonary diseases (pneumonia, tuberculosis, aspergillosis), endocrine disorders (Addison's disease, myxoedema, hypopituitarism). It may also be secondary to medications and tumours (lung carcinoma, pancreatic carcinoma, thymoma), notably bronchogenic carcinoma of the 'oat cell' type (Robinson *et al.* 1980) The patient we report had SIADH associated with adenocarcinoma of the endometrium. The electrolyte disturbances were promptly corrected by total hysterectomy and bilateral salpingo-oophorectomy.

The physiological control of ADH secretion is under both osmotic and non-osmotic regulation. Individual variation, genetic, environmental, species differences, and the nature of the solute providing the osmotic stimuli can significantly affect the release of the hormone by altering the threshold and/or the sensitivity of the hypothalamic osmoreceptor (Schrier *et al.* 1979). Vasopressin secretion is also controlled by an anatomically separate pathway which is responsive to non-osmotic stimuli. It appears that both low-pressure (left atrial) and high-pressure (carotid and aortic) receptors via the parasympathetic pathways provide the major non-osmotic pathway for vasopressin release. Such pathways are activated in response to acute systemic haemodynamic changes, stress, and hypoxia (Schrier *et al.* 1979).

SIADH is diagnosed when ADH secretion persists despite the absence of known osmolar and non-osmolar stimuli, as in our patient.

This patient fulfilled many of the criteria for SIADH. Hyponatraemia occurred in the presence of inappropriately elevated urine osmolality. There was no evidence of dilutional hyponatraemia due to adrenal insufficiency, salt-losing nephritis, diarrhoea, or previous diuretic therapy. Hyponatraemic oedema states such as congestive heart failure, cirrhosis or nephrosis were also excluded. There was no excessive water intake. The low BUN level, the absence of haemoconcentration and the high urine sodium concentration made dilutional hyponatraemia unlikely. The antidiuretic state in this patient was partially relieved by water restriction and permanently corrected by removing the uterine malignancy. Although no tissue specimens were obtained for ADH assay, the clinical course suggested that the tumour was responsible for the state of inappropriate antidiuresis.

Patients with SIADH represent a heterogeneous group of disorders with various patterns of ADH release. There are four patterns (Robertson 1983): Type A in which secretion is erratic and seemingly independent of osmoreceptor function; Type B with a lowered threshold for vasopressin release—a reset osmostat; Type C whose plasma vasopressin is inappropriately increased under basal conditions but remains constant during hypertonic saline infusion until plasma osmolality begins to exceed the normal osmoreceptor threshold, beyond which plasma vasopressin begins to rise normally, in close correlation with plasma osmolality and Type D characterized by low ADH levels, where presumably there is an ADH-independent urinary diluting defect or an enhanced sensitivity to the hormone.

A variety of possibilities has been postulated from what is known about the secondary effects of malignancy and the factors that can alter osmoreceptor function. Lung cancer might lower the set of the osmostat by obstructing venous return, thus producing effective hypovolaemia (Dossetor *et al.* 1961). Interference with baroreceptor input by mechanical or toxic effects of the tumour might also reset the osmostat, since vagotomy is known to mimic the effect of hypotension or hypovolaemia by removing the tonic inhibitory tone normally exerted by the baroreceptors (Schrier *et al.* 1972; Thames & Schmid 1979). Finally, the tumour might also elaborate agonists or antagonists of natural neurotransmitters that directly affect the set of the osmoreceptor system (Miller 1980; Kamoi *et al.* 1979). Various work associated with bronchogenic carcinoma also suggested production of ADH by the tumour itself (Bower *et al.* 1964) and large quantities of antidiuretic material has been demonstrated in tumour assays (Amatruda *et al.* 1963).

Production of hormones (or of analogous, physiologically active substances) by a variety of malignant tumours is now well recognized. Malignant tumours have been shown to produce parathyroid hormone (Greenberg *et al.* 1964), 5-hydroxy-tryptophan (Gowenlock *et al.* 1964) and adrenocorticotrophic hormone (Bower &

Gordon 1965). Ectopic human chorionic gonadotrophin secretion by a highly anaplastic adenocarcinoma of endometrium has also been reported (Tsoutsoplides 1980). We are not aware of any previous report of SIADH in association with adenocarcinoma of endometrium.

Acknowledgment

We thank Mrs R. Lo for her clerical assistance.

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CORRESPONDENCE

Müllerian adenofibroma. Case report

Dear Sir,

I am writing to comment on this recent case report by Hilton, Tacchi and Watson [*Br J Obstet Gynaecol* (1984) **91**, 1261–1265] because I feel that some confusion has arisen about the criteria for malignancy in mesenchymal tumours of the uterus and, in particular, I question whether this example of an unusual tumour has been correctly diagnosed. By far the most important factor in deciding malignant potential in these tumours is, as the authors acknowledge, the number of mitotic figures, so a mitotic count has to be undertaken. This figure is customarily recorded as mitotic figures per 10 high-power fields. The authors have misquoted both Silverberg (1976) and Hendrickson & Kempson (1980), the latter regarding three mitotic figures per *10* high-power fields (not three mitotic figures per high-power field) as indicative of malignancy in the presence of nuclear pleomorphism and anaplasia. This 10-fold difference is, of course, very significant!

Turning now to the example being reported, the authors state that 'In 200 high-power fields examined the mean incidence of mitoses was one per field (range 0–4)'—that is, 10 mitotic figures per 10 high-power fields, which is malignant by all current standards. If this is so, then the tumour reported is a Müllerian adenosarcoma. I feel, furthermore, that the degree of nuclear pleomorphism shown in Fig. 4 is in keeping with this high mitotic count and I would suggest that the prognosis for this patient might not be as favourable as the authors imply. Alternatively, it is possible that the number '10' has been omitted, both from the description of the case being reported and in the references to Silverberg and Hendrickson & Kempson. In this case, this letter serves to point out to readers that they should disregard the figures quoted for mitotic counts in this article.

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Author's reply

Dear Sir,

I am grateful to Dr M. C. Anderson for drawing attention to the regrettable error which intruded into the manuscript of our paper. Throughout the text the figures for the incidence of mitoses, which are expressed per high-power field, should have been given in terms of the conventional unit area of 10 high-power fields. In the tumour which we described the mean incidence of mitoses was *one per 10 high-power fields,* a value which is consistent with our assessment of the tumour as a Mullerian adenofibroma rather than an adenosarcoma.

Unlike Dr Samuel Johnson, who erroneously defined *pastern* as 'the knee of the horse' we do not plead 'sheer ignorance', but rather a reprehensible negligence in proof reading. For this we apologise to you and your readers. As regards Dr Anderson's assessment of Fig. 4 in our case report we feel that this is necessarily a matter of subjective interpretation which may have been influenced by the confusion about the true frequency of mitoses and by the numbers of pyknotic nuclei masquerading as mitoses. The patient has now survived for over 3 years since her hysterectomy and we remain hopeful about the long-term prognosis.

A. J. Watson
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Are vaginal fluid concentrations of prolactin, α-fetoprotein and human placental lactogen useful for diagnosing ruptured membranes?

Dear Sir,

Huber *et al.* (*Br J Obstet Gynaecol* (1983) **90**, 1183-1185) assayed prolactin, α-fetoprotein and human placental lactogen in vaginal secretions as a means of diagnosing ruptured membranes. They conclude that these assays are of no value as there is too much overlap between patients whose membranes were intact, and those who had ruptured membranes. For the following reasons, we feel they have prematurely abandoned the technique.

First, the investigators study only patients at term. For these patients, accurate diagnosis is far less crucial than in the premature patient for whom the decision for or against conservative therapy is crucial. Amniotic fluid α-fetoprotein (AF-AFP) decreases as gestational age advances (Weiss *et al.* 1976). The earlier the gestation, and therefore the more important an accurate diagnosis, the higher the AF-AFP. We (Rochelson *et al.* 1983) studied 99 patients with ruptured membrane for α-fetoprotein obtained vaginally. No patient under 35 weeks had an AF-AFP under 100 ng/ml. Of 25 vaginal secretions studied at varying gestational ages, none had an AFP value over 15 ng/ml. Thus the case Huber *et al.* (1983) make against AFP determination at term may not be valid in the premature patient

Secondly, the authors do not address the diagnostic value of a high AFP. As in our study, they found no vaginal secretions over 15 ng/ml. Setting this as a diagnostic threshold, 21 cases of ruptured membranes in their study would be diagnosed correctly, and 12 would be false-negatives. There would be no false-positives, therefore no pregnancy would be inappropriately terminated. The more appropriate conclusion to the data presented would be that whereas a high AFP is diagnostic of rupture of the membranes, a low value is not helpful. Although the predictive value of a negative test is poor, that of a positive test (AFP>15 ng/ml) is 100%.

Thirdly, the authors do not address the issue of a multivariate analysis of the data. While they mention that a 'low value for one protein was rarely associated with a low value for a second one, and never with the other two', there is no consideration given to combining results to improve the accuracy of the test.

It is true that none of these tests individually is the ideal for the diagnosis of premature rupture of the membrane at term. However, by the use of a combination of methods, or in patients under 36 weeks, results may be improved.

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Fetal death following extra-amniotic prostaglandin gel. Report of two cases

Dear Sir,

We have read with interest the two case reports by Quinn & Murphy (*Br J Obstet Gynaecol* (1981) **88**, 650-651) concerning intrauterine deaths occurring after extra-amniotic instillation of a single dose of 10 mg $PGF_{2\alpha}$ in Tylose gel for pre-induction cervical ripening. Our experience with the technique described by Calder *et al.* (1977) is rather extensive and in about 1500 women who have received the standard dose of 0·5 mg of PGE_2 in 10 ml of 8% Tylose gel for elective ripening of the cervix and/or to induce labour no fetal deaths have occurred. But we have knowledge of two patients in whom administration of 5 mg of $PGE_{2\alpha}$ in the same type of viscous gel base was followed by uterine hypertonia and severe fetal hypoxia leading to fetal death in one and early neonatal death in the other. The cause, admitted by the gynaecologist, was defective mixing of the active compound with the gel before instillation. Although it is not possible to deduce the actual cause of fetal death in the reports by Quinn & Murphy (1981), we wish to caution physicians against applying PG dosages that are unnecessarily large for the purpose. The dose of PGE_2 currently applied in our clinic corresponds roughly to 4–5 mg $PGF_{2\alpha}$, which is about half of that used by the authors.

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BOOK REVIEWS

Obstetrics and Gynaecology Annual 1984 Vol 13 edited by Ralph M. Wynn. Prentice/Hall International, Hemel Hempstead, 1984, 339 pages with figures and tables, £40.40

People love annuals. From the Beano Book to Whitaker's Almanack, a date on the cover makes a book desirable, like a car with new number plates. Lay publishers generally put the next year's date on their annuals, but since this would lend a kind of Old Moore quality to a medical textbook, the *Obstetrics and Gynaecology Annual 1984* came out during the year to which its title refers. This is the 13th volume of the series and the editor, Ralph Wynn of Chicago, provides no preface, evidently feeling that introductions are now superfluous. The authors are mainly from the eastern states of the USA, though one is from as far west as Nebraska and one—the only overseas contributor, Harold Fox, writing on endometrial hyperplasias—is from Manchester, UK. The 14 subjects, equally divided between obstetrics and gynaecology, are adroitly chosen to appeal to a wide variety of clinicians and, rightly, reflect current American preoccupations. With circumcision rates apparently between 70% and 95% among newborn males in the United States, an 'update' on this controversy seems desirable: the authors, writing with that wary tact used by British authors discussing birthing positions, conclude that 'neonatal circumcision cannot be considered as a cut and dried issue' and call for better scientific studies. With caesarean section rates in the US between 10·1% and 22%, there is a discussion on how to minimize complications and unnecessary operations. With divorce rates between 1 in 3 and 1 in 2, there is an interesting chapter on the physical and mental symptoms of 'divorce distress'. Over the last 10 years the proportion of American women breastfeeding on discharge from hospital has risen from 25% to 50%, and the chapter for doctors unused to giving advice on suckling is timely and well-written. Other topics of current interest on both sides of the Atlantic include AIH and the clinical use of gonadotrophin-releasing hormone, and those of timeless fascination include diabetes in pregnancy and polycystic ovarian disease. An annual not just for Americans, and not just for 1984.

James Drife

Fetal Physiology and Medicine Second Revised Edition edited by Richard W. Beard & Peter W. Nathanielsz. The Butterworth Group, Sevenoaks, 1984, 823 pages with figures and tables, £70.00

The first edition of *Fetal Physiology and Medicine* (1976) recognized that clinical obstetrics and fetal physiology needed each other. Nine years and many clinical 'advances' later they perhaps need each other even more. This new edition, under the same editorial partnership of Richard Beard and Peter Nathanielsz, now appears as volume 6 in the 'Reproductive Medicine' series. Not that this book needs a niche—it really does stand on its own merits as a most informative and scholarly review of fetal physiology. There are over 40 contributors mostly from Britain and United States, with some distinguished researchers from other parts of Europe and Australia enriching the cosmopolitan flavour. It is fortunate that wherever you go physiology is physiology—it has a kind of basic truth that transcends parochialism. The 24 chapters in this new and completely revised edition embrace a wide spectrum of subjects including sexual differentiation, immunology, metabolism, energy requirements, growth, endocrinology, placental transfer of minerals, and cardiopulmonary physiology. Although of necessity a lot of animal work is referred to, the contributors have wherever possible included relevant human studies. A blend of 'physiology' and 'disease' has been successfully achieved, thus ear-marking the book for clinicians as well as physiologists—exemplified incidentally by chapters on diabetes mellitus, infection, the epidemiology of perinatal wastage, various aspects of fetal monitoring, and adaptation in the newborn. The book demands very careful study and is not for 'intercity' or bedside reading. Nonetheless, the contributors and the editors must be given credit for clarity of expression in the face of such adversities as the ontogeny of the cellular immune response. As always in a book covering so many subjects it would be invidious to select individual chapters for comment—but I will. The opening chapter on the diagnosis of structural abnormalities with ultrasound is new to the second edition. To some of us, one antenatal ultrasound picture looks very much like another—rather like discovering that Picasso had a gray phase; but the scans in this chapter are accompanied by most helpful black and white sketches. The authors include brief but important clinical information about many of the visualized malformations. Another new chapter in this edition is Hobel's 'prevention of preterm birth'. His review on the epidemiology and aetiology of preterm birth is splendid, but the piece on prevention is brief and leaves the reader wanting more. The identification of 'risk' (and we must acknowledge Hobel's experience in that field), coupled with intervention programmes which have a social slant are irresistible and common-sense approaches to prevention. But can we afford to be optimistic when good supportive data remains so thin? What's going wrong? Perhaps in the next edition we might read about this—unless of course it has all come right by then.

Malcolm Chiswick

Clinical Pathology of the Endocrine Ovary edited by J. de Brux & J.-P. Gautray. MTP Press Limited, Lancaster, 1984, 184 pages with figures and tables, £29.95

Of all the endocrine glands, the ovary and placenta have been most readily available for direct study. In the course of a year, scores of placentas and ovaries must pass through the hands of the average obstetrican and gynaecologist. It is surprising therefore that, in spite of the extensive interest shown by pathologists, clinicians have taken so little interest in its functional morphology. With a few exceptions this book illustrates how little impact the major advances in our understanding of the physiology of ovarian function has on the disorders of ovarian function which present clinically The editors, Drs de Brux and J.-P. Gautray from the Faculty of Medicine, Université Paris have assembled a group of distinguished experts who contribute chapters on the basic physiology of the ovary. Perhaps the most important contribution to our knowledge has been the realization that, in addition to control by pituitary gonadotrophins, there are a whole host of intra-ovarian regulatory factors which determine the sensitivity of individual follicles to gonadotrophins. Although it has been known for over 50 years that the concentration of oestradiol in follicular fluid was 1000-fold greater than in other tissues, its local function was unknown. In a series of comprehensive experiments in the rat, Jo Anne Richards and her colleagues established the key role that oestradiol plays in stimulating proliferation of the granulosa cells of the developing follicle. In addition, it amplifies the stimulatory effects of FSH in generating the synthesis of FSH and LH receptors. In this way the follicle becomes progressively more sensitive to circulating gonadotrophins. The high concentration of oestradiol in follicular fluid also probably influences the development of the oocyte. The oocytes within the follicle remain arrested in the dictyate stage of the second meiotic division until activated by LH just prior to ovulation. If the oocyte is removed from the follicle prematurely it will mature spontaneously *in vitro* although its capacity to undergo fertilization and normal embryo development is impaired. Nina Channing and her colleagues have identfied a number of factors including oocyte maturation inhibitor (OMI) produced by the granulosa cells which influence the activity of the oocyte. However, the exact chemical identification of these factors and their role in human physiology remains to be elucidated. Probably the chapter of most interest to clinicians in the physiology section is that by Dr Gougeon on the dynamics of follicle growth. This chapter is based on a painstaking analysis of 33 pairs of ovaries collected from women undergoing gynaecological surgery. By relatively simple but tedious morphometric analysis, Gougeon was able to classify 2125 follicles into eight classes depending on size, number of granulosa cells and pyknotic nuclei. By measuring the mitotic index as an index of growth rate, he was able to determine the relative growth of different classes of follicles at different stages of the menstrual cycle. It is worth buying the book for the succinct and clear report of this important and novel study alone. The clinical pathology section attempts in the first chapter on the evolution of non-ovulatory follicles to apply some of the knowledge of basic physiology to pathology. There is, however, a scarcity of direct functional studies on pathological ovaries and many of the chapters in this section have a fairly old fashioned ring. The chapters on the postmenopausal ovary ignore some of the recent work on its biosynthetic potential and secretion *in vivo,* but rely on classical histology and histochemistry. Surprisingly, there is virtually no mention of the polycystic ovary about which much has been published in functional terms. The chapter on the ovary in pregnancy is a simple short summary of some of the changes which can occur but is without references and, again, says nothing about its role in the physiology of pregnancy. Finally, there is a short section on 'clinical physiopathology' which includes luteal phase defect and gonadotrophin-resistant ovaries. These chapters do little more than repeat much of the unsubstantiated theories about these two clinical entities without reviewing critically the scanty evidence available about their aetiology. In many ways this is a disappointing book but is saved by some excellent chapters summarizing the physiology of the ovary.

David T. Baird

Postnatal Exercises. A Six-month Fitness Programme for Mother and Baby Barbara Whiteford & Margie Polden. Century Publishing Co. Ltd, London, 1984, 128 pages fully illustrated, £4.95

The title of this book, *Postnatal Exercises,* does not do justice to its contents. Here we have a useful guide for lay people for the 6 months which follow the birth of a baby. The authors deal not only with a graded range of maternal exercises, but also with the development of a newborn infant and with many of the psychological, emotional and physical problems which occur in the 6 months after childbirth. They communicate with the reader in simple, warm and unpatronizing terms and one senses the experience the writers have had in physiotherapy and parenthood. The text is well illustrated by Sandra Lousada's black and white photographs and also by drawings, and at various stages in the book useful daily exercise programmes, based on preceding text and illustrations, are presented. There is a good index and also a helpful page of information giving further reading and addresses which might be useful to a new mother. Those who practise obstetrics and midwifery would do well to recommend this moderately priced and attractive book to their clients who, having been the focus of attention before and during childbirth, tend to be neglected afterwards.

F. E. Loeffler

Clinics in Obstetrics and Gynaecology Vol 11/No 2, The Small Baby edited by P. W. Howie & N. B. Patel. W. B. Saunders, London, 1984, 252 pages with figures and tables, £12.50

This issue attempts to summarize the current state of knowledge on the problems of the small baby and to point towards future development. The editors have achieved their objective. The book is relatively short, comprising 12 chapters equally divided between the preterm and growth-retarded baby. Chamberlain gives a succinct outline of the epidemiology and aetiological factors associated with the preterm baby based mainly on data from the 1970 British Births Study. Papiernik writes a provocative chapter on the prediction of preterm labour. His methods are time-consuming, but he seems to have a high degree of success. He admits, however, that the ability to predict gains importance only as part of a wider objective, the prevention of preterm birth. Since this involves persuading women to change their life styles and conditions, it is unlikely to be achieved easily. Short chapters by Ingemarsson and Whittle, respectively, bring us up to date on the pharmacology of tocolytic agents and lung maturation. It is sad that earlier hopes of a break-through in this area have not been fulfilled. Howie and Patel give a practical and balanced view of the obstetric management of preterm labour; as do Cashore and Stern on the care of the preterm baby. Keirse discusses the difficulties of defining fetal growth retardation, and the use of appropriate standards. It is sad, that he has not mentioned any biological factors among the 'potential causes of intrauterine growth retardation'. Klopper's chapter indicates that there has been little progress in solving the problem of the biochemical assessment of retarded fetal growth; whereas Geirsson and Persson clearly demonstrate the great advances made in ultrasonic techniques for fetometry, and their potential value as functional tests. In their chapter on obstetric management Simpson and Creasy describe a biophysical profile for monitoring high-risk pregnancies. Discussing the timing of delivery they cite some studies suggesting that when intrauterine growth retardation is severe, prolonging the unfavourable intrauterine milieu may increase long-term developmental morbidity, particularly when there is associated hypertension. The present reviewer also has data to support this view. Jones and Roberton outline the potential problems of SFD babies. Evidence from their own unit shows that, given prompt and active attention at delivery and in the subsequent few hours, SFD infants are at very low risk of neonatal disease. David Taylor, writing on low birthweight and neurodevelopmental handicap, was clearly not aware of recent studies on SFD children born in the 1970s. Their prognosis, now, is much more favourable than for those born in previous decades. This is a well-balanced book; tightly written, clearly illustrated, and with plenty of up-to-date references. It should be mandatory reading for MRCOG candidates; and research workers in this field will find it useful. Obstetricians in active practice will already be cognisant of most of the contents, but could profitably leaf it over before putting a copy in the departmental library.

Margaret Ounsted

Books received some of which will be reviewed at a later date

A Practical Guide for the Obstetric Team by M D Read & Diana Wellby John Wiley & Sons, Chichester, 1985, 285 pages with figures and tables, £9.75

Principles and Practice of Obstetric Anaethesia Fifth Edition, by J Selwyn Crawford Blackwell Scientific Publications, Oxford, 1984, 448 pages with figures and tables, £32 50

Massachusetts General Hospital Department of Nursing Gynecological Standards of Care edited by Elizabeth A. Davis. Prentice/Hall International, Hemel Hempstead, 1984, 374 pages, £28 75, US$33 75

Lecture Notes on Obstetrics Fifth Edition, by Geoffrey Chamberlain. Blackwell Scientific Publications, Oxford, 1984, 388 pages with figures and tables, £7 50

The Biochemical Effects of Drugs in Pregnancy Vol 2 by A Onnis & P Grella. Ellis Horwood, Chichester, 1984, 495 pages with figures and tables, £45.00

The Captured Womb, A History of the Medical Care of Pregnant Women by Ann Oakley. Basil Blackwell, Oxford, 1984, 352 pages with figures and tables, £17 50

Reviews in Perinatal Medicine Volume 5 edited by E M Scarpelli & E. V Cosme. Alan R. Liss, New York, 1984, 214 pages with figures and tables, £32.00

In Vitro Fertilization and Embryo Transfer edited by Alan Trounson & Carl Wood Churchill Livingstone. Edinburgh, 1984, 254 pages with figures and tables, £25 00

Williams Obstetrics 17th Edition, edited by J. A. Pritchard, P. C MacDonald & N. F Gant Appleton-Century-Crofts, Connecticut, 1984, 976 pages with figures and tables, £39.95

The Principles and Practice of Ultrasonography in Obstetrics and Gynecology Third Edition, by Roger Sanders & A. Everette James. Appleton-Century-Crofts, Connecticut, 1984, 663 pages fully illustrated, £86 30, US$101 25

Obstetrics for the House Officer by William F Rayburn & Justin P Lavin Jr Williams & Wilkins, Baltimore, 245 pages with figures and tables, £8.00

Research in Family Planning edited by J. Bonnar, W. Thompson & R F. Harrison MTP Press Ltd, Lancaster, 1984, 249 pages with figures and tables, £39.95

Biomedical Aspects of IUDs (Advances in Reproductive Health Care) edited by H Hasson, W A. A van Os & E S E. Hafez MTP Press Ltd, Lancaster, 1984, 142 pages with figures and tables, £45.00

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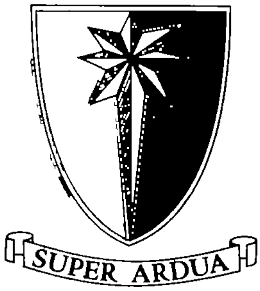

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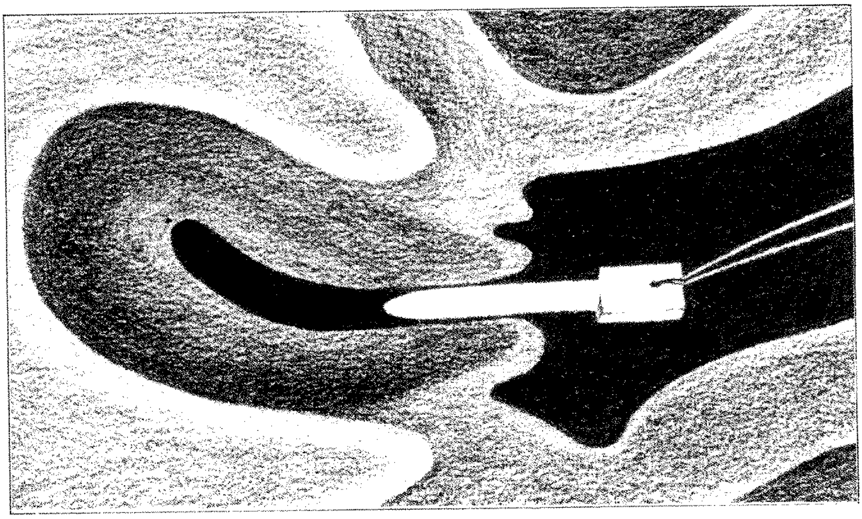

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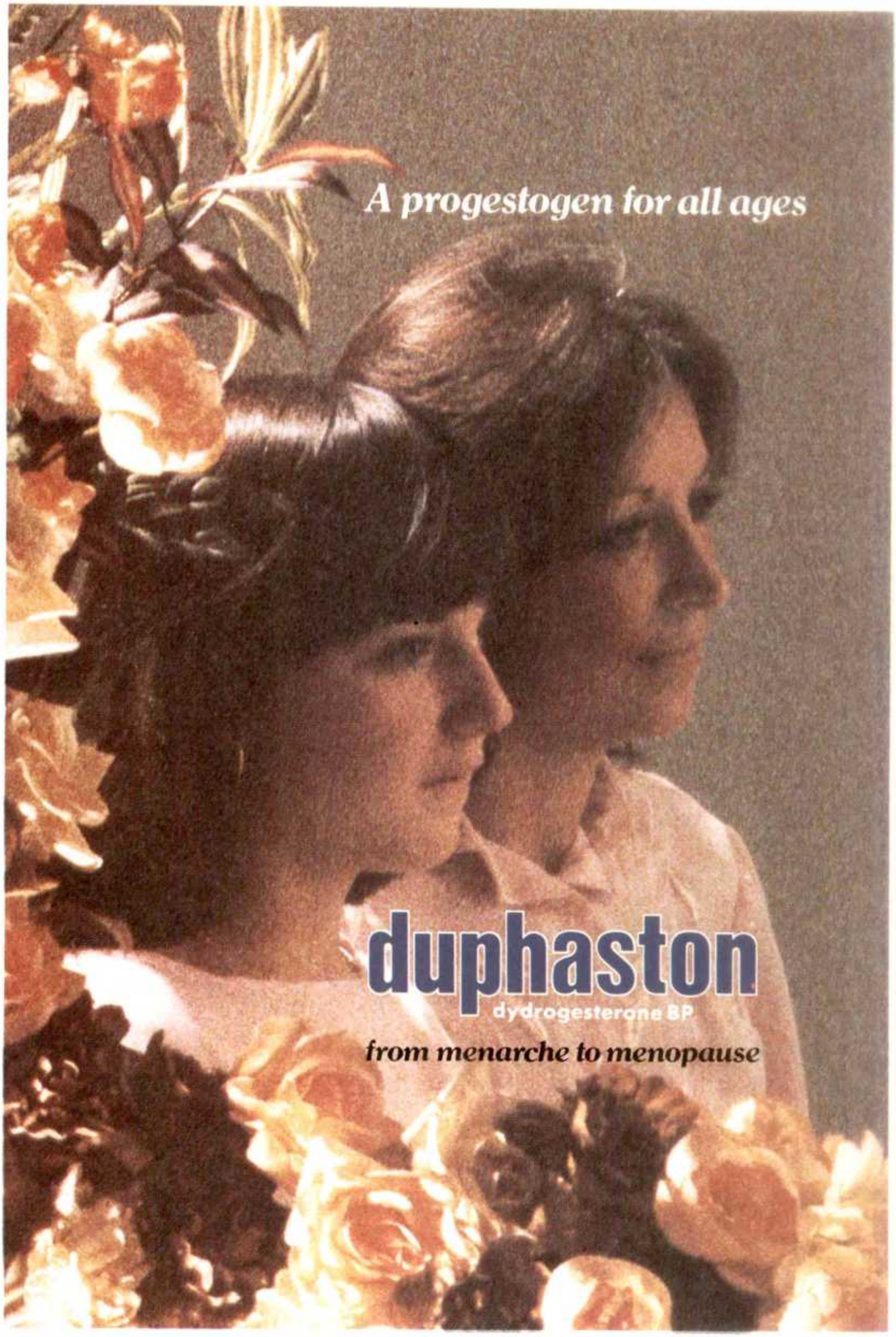

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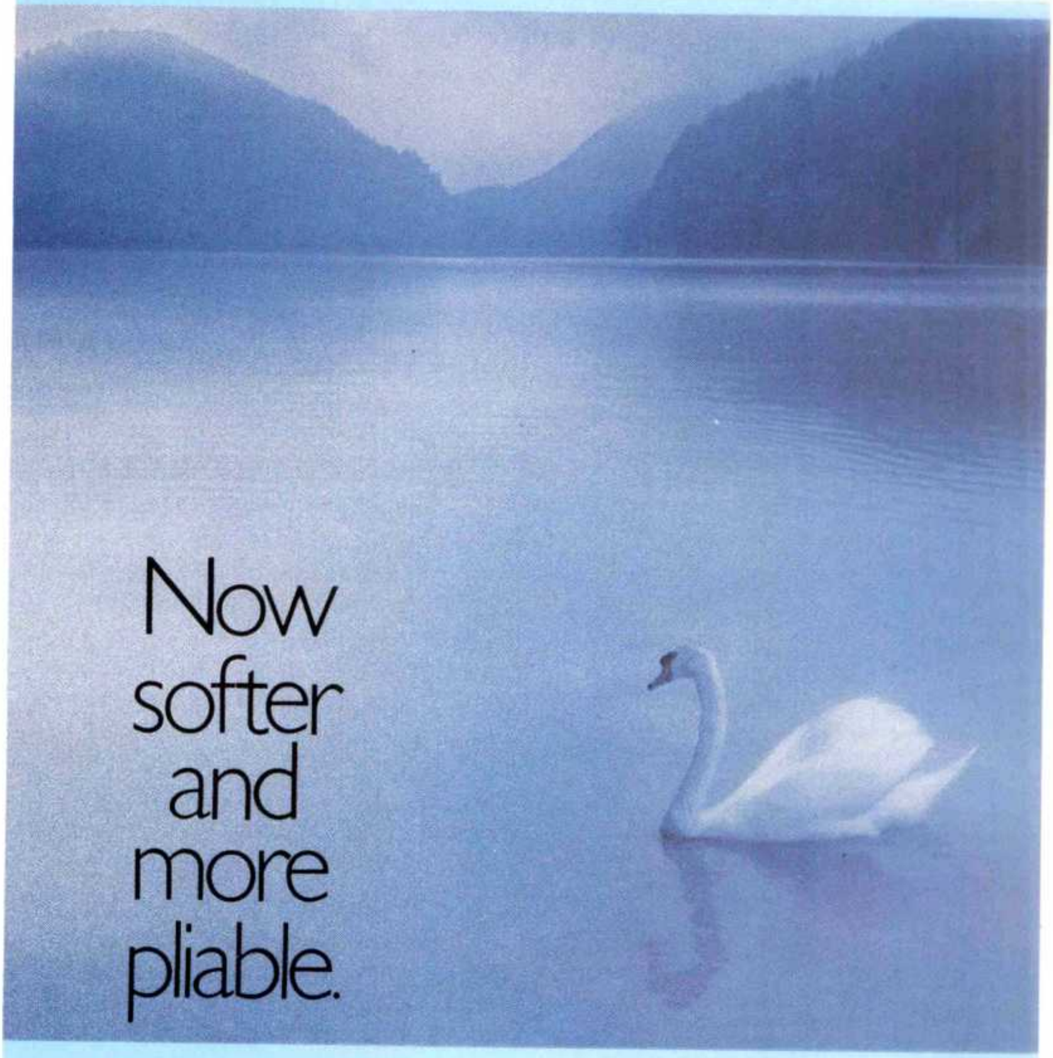

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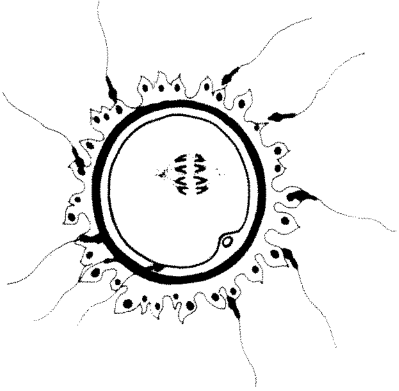
Edited by **W.R. Jones**
Department of Obstetrics & Gynaecology,
Flinders Medical Centre, Bedford Park,
SA 5042, Australia



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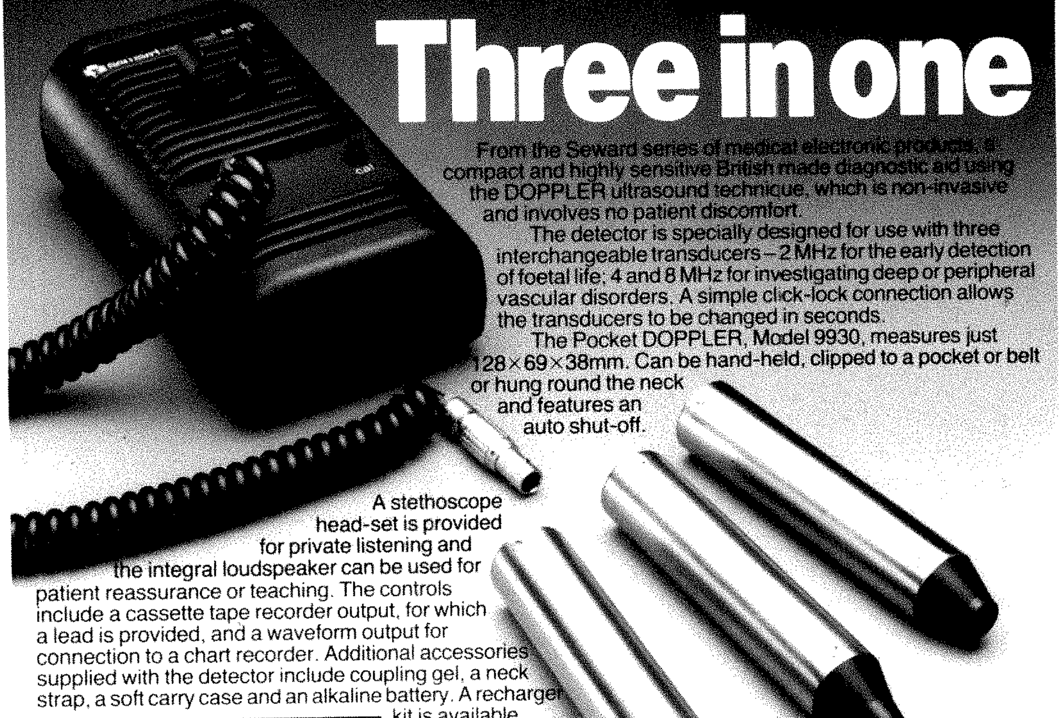

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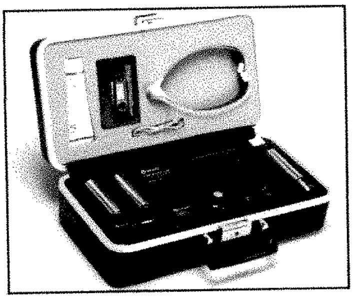

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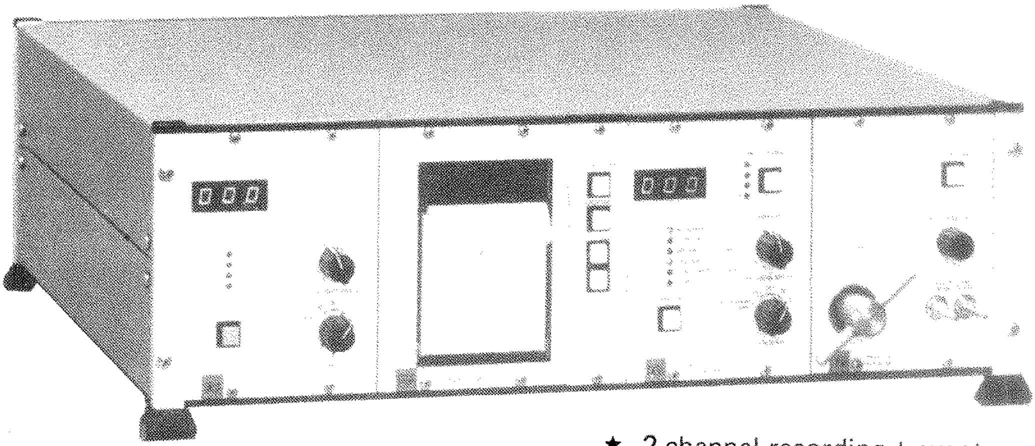

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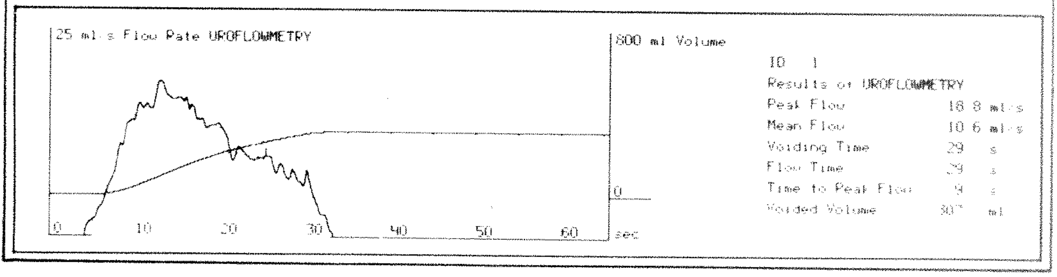

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COMMENTARY

Litigation in obstetrics and gynaecology

Nobody likes to talk about the pending litigation that involves them. After all, there must have been some complication or fault or perhaps even both that led to the action in the first place The fact is that most consultants in obstetrics and gynaecology have been sued, or are being sued or will receive the unwelcome attention of a litiginous patient in the near future and none of us quite realize how far things have already moved. Unfortunately, we have now joined the ranks of the big spenders in medical litigation and it is going to get worse.

Most gynaecologists care about their patients and they take an active pride in the quality and standards of their practice. If a mistake is made which amounts to substandard practice, very few doctors have any stomach for taking the matter to court and most would feel that the patient should receive compensation. The real problem starts when someone acts in good faith, exercises a standard of care that his or her peers consider satisfactory and yet the outcome is unsatisfactory. Everyone thought that Lord Denning had solved this problem with the Jordan case when all these matters were thoroughly discussed and it was held that a clinician acting with good intent and proper skill could not be considered to be negligent just on the grounds of a subsequent complication. The case has regrettably had little impact. It would appear that some judges tend to try to find reasons for helping the plaintiff on the basis that they have suffered a misfortune and therefore someone should recompense them for their pain and suffering. The judgement may have little relevance to the question of negligent management. Perhaps this did not matter a great deal when the settlements were small, but in cases of fetal brain damage, they are often huge. There is also a real danger that the clinician (merely on the dictum of 'res ipsa loquitur') may be held responsible for damage to an infant simply because he took a positive action to save a child's life. For example, if a labour progresses normally until the second stage and the fetus shows signs of distress, the clinician may apply forceps to expedite delivery only to find that the child is subsequently born with brain damage. The child may have sustained the damage some weeks before labour started, but if it survives, who can tell when the damage occurred? If the clinician does nothing and the child is brain-damaged, then he will certainly be considered to be at fault. There are a substantial number of new cases of fetal and neonatal brain damage now becoming subject to litigation, where there has been a normal spontaneous vaginal delivery in apparently uncomplicated labours.

The Medical Defence Union currently opens about 9000 new files per year relating to potential litigation, and of these cases, some 600 relate to obstetrics and gynaecology These files are generated from members all over the world Approximately 80 cases now relate to brain damage in the infant.

What happens when some huge settlement is awarded to the parents of some unfortunate brain-damaged child? Who pays the bill?

If the case is medical, then the profession pays the bill because Defence Societies are not insurance companies but are societies for the mutual self-help of doctors. The public may feel that it is perfectly reasonable to pass these costs on to the profession. After all, doctors are well paid and they can afford it. At present, the profession pays about 1% of their income in malpractice fees, but in the USA, the corresponding figure in obstetrics and gynaecology is about 25%. In the States, the costs are passed on to the client. In the United Kingdom that is not possible because the vast majority of doctors in this country are employed by the National Health Service and work on relatively fixed incomes.

Some insurance companies would like to enter the field with differential rates for the high- and low-risk specialities. Such a policy would have a disastrous effect on obstetrics and gynaecology because it would presumably not differentiate between the SHO undertaking his first job and the consultant and it would certainly have a deleterious effect on the already rather fragile recruitment to the speciality. Who really wants to pay a lot of extra money for the pleasure of entering a discipline that is probably the most physically demanding of occupations in the medical arena and is rapidly becoming the most litigation-prone discipline in medical practice?

If an employee of the Health Authority is involved and is the principal defendant, then the costs are met by the Health Authority who do not carry insurance and who meet the costs out of their general revenues. If there is a big settlement, it may mean the closure of a ward for a year and the postponement of necessary capital expenditure.

Perhaps it would not be so bad if it stopped at the purely fiscal level, but that is not the end of the story. Any obstetrician who has been taken through a courtroom knows what a disheartening, demoralizing and time-consuming business it is. Even if the case is successfully defended, there is often a lot of damaging local press reporting which invariably publicizes the first days of the proceedings and rarely prints the outcome unless it involves a large settlement in favour of the plaintiff. The impact of all this on the consultant and his junior staff and the hospital is to engender an ever more defensive attitude to practice—more investigations, more operative intervention and less and less opportunity to test the efficacy of existing methods of management

An American colleague recently remarked that it was his standard practice if there were any complications on his obstetric wards to call in and see the hospital lawyers as soon as his daily ward round was complete

We are rapidly following the same route There are alternative approaches such as no fault compensation or even encouraging patients to take out their own insurance against medical accidents.

One thing is certain—we are heading for a disastrous American-style litigation scene There must be a better way to do business.

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The routine use of ultrasound

Two recent papers have considered the possible value of routine ultrasound The first is the Report of the Royal College of Obstetricians and Gynaecologists' Working Party (1984). The second is published by Thacker in the current issue of the *Journal* on page 437. Both of these reports come at a very appropriate time, but unfortunately leave important questions unanswered. While the College report rehearses the possible advantages of ultrasound, the scientific analysis does not show the rigour which would normally be expected of its Scientific Committee The paper by Thacker, by contrast, is a valuable guide to the planning and assessment of randomized trials, and uses the published trials of ultrasound to illustrate the general issues. But it does not provide a comprehensive review of the advantages or disadvantages of routine scanning.

Thacker has carried out a meticulous analysis of the four published randomized trials of routine scanning. He points out that, because of the small sample sizes involved, these studies could only be expected to detect differences in the frequency of common end-points such as induction of labour and hospital admission. Although Thacker has pooled data from three of these trials, his power calculations demonstrate that the combined sample size remains inadequate in respect of many important outcomes.

The report from the Royal College, on the other hand, ignores the issue of test-power altogether. It makes much of the study of Eik-Nes *et al.* (1984), who found three perinatal deaths in a routinely screened group of patients compared with eight deaths amongst randomized controls. Clearly this is a difference which could easily be ascribed to chance. Indeed this possibility might have been clearer if the authors had pointed out that three of the deaths among the controls occurred in the late neonatal period and would thus be unlikely to be attributable to a lack of ultrasound in early pregnancy. This section of the College report also gives a falsely optimistic impression of the accuracy of ultrasound detection of growth retardation, quoting sensitivities of up to 92%, and ignores the issue of predictive value (Chard & Lilford 1985) which we shall discuss presently.

The College report deals with a number of specific conditions such as placenta praevia which, it states, complicates 0·5% of all pregnancies. It goes on to suggest that 5% of second-trimester pregnancies have an apparently low-lying placenta and that, of these, 5% will be confirmed to have this condition at a later stage. These figures taken together imply a 50% false-negative rate for the second trimester detection of placenta praevia and clearly this point should have been discussed at greater length.

The section on maternal serum α-fetoprotein (AFP) screening in the College report is both confusing and contains serious errors. First, it is stated that the specificity of a screening programme depends on the prevalence of the disorder being sought. This is not so (Department of Clinical Epidemiology and Biostatistics, McMaster University 1983). It is the predictive value (both positive and negative) of a test that is crucially dependent on prevalence or prior probability Specificity will only change with prevalence if the severity of the disorder changes as it becomes more common. The authors continue with the statement that 'this means that by using 2·5 times the multiple of the median as the cut-off point, the chances of a high maternal serum AFP result being caused by spina bifida would only be 2·5%' There is in fact no inherent reason why a given multiple of the median should imply a particular predictive value. It just so happens that the variance of AFP measurements is such that 2·5 times the median corresponds roughly to 97·5 centile. Thus, very approximately, 2·5% of the population will have a raised maternal serum AFP level. If we assume the authors' extremely low prevalence of 1/1000 and an 80% sensitivity of maternal AFP screening, then the chance of a high result being caused by spina bifida would be 3·2%.

$$\frac{\text{True positive}}{\text{True positive+False positive}} = \frac{0{\cdot}8}{(0{\cdot}8+24{\cdot}2)}$$

In fact, in most parts of the UK, where the prior probability of spina bifida is 1/1600, the predictive value would be closer to 7%. These objections do not negate the Committee's overall conclusions that ultrasound (in centres of excellence) is a more sensitive and specific test, but they do detract from the scientific credibility of the report as a whole. Another disturbing aspect of the report is that it relies heavily on the results of studies conducted at King's College Hospital, while ignoring much of the less flattering literature (Roberts *et al* 1983; Hibbard *et al.* 1985)

The College report stresses the benefits claimed for routine scanning, including more accurate prediction of the spontaneous onset of labour, earlier diagnosis of twins and placenta praevia and the recognition of congenital abnormalities. But we believe the authors should also have pointed out that ultrasound scanning, like all new technology, does carry certain disadvantages. These include the unnecessary but inevitable parental anxiety that follows both uncertainties raised by ultrasonograms which are difficult to interpret and the discovery of features such as choroid plexus cysts, pelvi-ureteric junction obstruction and macerated second twin, which are usually associated with a good pregnancy outcome. Nor does the report address adequately the inappropriate intervention which is sometimes prompted by ultrasound findings! Thacker points out that these may be important when he states that 'human and monetary costs must also be assessed'; but he does not offer any advice on how this might be done. An approach adopted recently by Hibbard *et al* (1985) is probably more realistic than the massive controlled trial advocated by Thacker. The power calculation quoted by Thacker shows that 6250 women would be required in each arm of the trial to show a reduction in perinatal mortality from 10 to 5 per 1000 (with a power of 90% at the 5% level of significance). This calculation is mathematically correct but it is unrealistic to think that one item of technology on its own could secure such a massive reduction. A more realistic assumption is that two of the 10 deaths per 1000 are due to congenital abnormalities and two are due to growth retardation. Routine ultrasound in early pregnancy, repeated in the third trimester, might be expected to identify half of these. The calculation would then be based on a reduction from 10 to 8 per 1000 and this would imply a trial with 46 820 women in each arm.

It is regrettable that neither of these two publications—the recent College report nor the excellent but limited review article—provide a clear and authoritative lead to the profession and decision makers

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Quality of controlled clinical trials. The case of imaging ultrasound in obstetrics: a review

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Summary. Randomized controlled trials are increasingly used to assess clinical practices in obstetrics and gynaecology. The strength of these studies is that they usually address the issue of selection bias satisfactorily. Yet, as with any form of scientific investigation, the randomized controlled trial has inherent limitations and is subject to flaws in its conduct. Using basic methodological criteria, this report assesses the quality of the four published controlled trials in which a policy of routine imaging ultrasonography in pregnancy was compared with a more restrictive policy. In addition, a pooled analysis using data from all four trials was conducted to illustrate how increasing the sample size may reveal differences between the two policies which remain undetected in trials using small samples. The researchers in these studies reached different conclusions as to the effectiveness of routine ultrasound screening. Taken together, these four trials provide valuable information about routine ultrasound screening but fail to demonstrate adequately the usefulness of imaging ultrasound as a screening procedure for all pregnant women. The assessment criteria presented here could be used by investigators, editors, referees and other readers as a guideline for assessing the quality of therapeutic studies upon which clinical practice should be based.

The randomized, controlled trial is generally accepted as the ideal method to assess the efficacy of clinical interventions in human populations (Cochrane 1971). Of course, trials are not always feasible (e.g., studying very rare diseases) and like any human endeavour are subject to flaws in conduct and errors in (Feinstein & Wells 1977) Hence, it is essential that clinicians understand the strengths and limitations of the controlled trial and develop methods to assess the results of published studies. This understanding becomes particularly important when the results of trials come to apparently contradictory conclusions. Just such a situation has arisen recently with the publication of four clinical trials designed to assess the value of the routine use of imaging ultrasound in pregnancy. One of these trials was conducted in London (Bennett *et al.* 1982), two in Norway [Eik-Nes *et al.* (1984) in Alesund and Bakketeig *et al.* (1984) in Trondheim] and one in Glasgow (Neilson *et al.* 1984). Three of these trials reported no evidence of benefit to women undergoing routine screening procedures (Bennett *et al.* 1982; Bakketeig *et al.* 1984; Neilson *et al.* 1984) whereas the fourth (Eik-Nes *et al.* 1984) concluded that screening decreases unnecessary induction as well as reducing perinatal morbidity and mortality. The purpose of this review is to describe a systematic approach to the assessment of clinical trials and to apply that method to the trials designed to assess the routine use of imaging ultrasound.

Assessing a clinical trial

There are several approaches to the assessment of trials, but certain basic elements are critical to adequate interpretation of results (Mostellar *et al.* 1980; Chalmers *et al.* 1981). The 14 criteria given in Table 1 are essential to a clear understanding of the conduct and analysis of a trial designed to assess a screening procedure This format is designed to clarify for the reader the important aspects of a particular trial. No scoring or weighting system is intended by such a table. In completing Table 1, an effort was made to obtain unpublished information from the authors so as to give readers a more complete picture of the available knowledge.

Prior hypotheses and statistical power

Greatest emphasis should be given to those results related to hypotheses for which a study is designed. Prior hypotheses were precisely stated in the Trondheim and Glasgow trials, but these hypotheses were used to calculate statistical power (the probability that a study will detect a true difference between two populations) and to estimate sample size in only the Trondheim study (Table 1).

Eligibility criteria

In the Alesund study, criteria for women entering the trial were non-exclusive, whereas the distinction between high-risk and low-risk pregnancies was not readily apparent in the other reports. In the absence of explicit criteria for risk, comparisons of the low-risk population in Glasgow with the other studies is difficult.

Allocation of subjects

This was done using formal randomization with opaque, sealed envelopes in the Norwegian trials, but by alternating hospital numbers in the British trials. The latter method is subject to selection bias and for this reason is less desirable (Mostellar *et al.* 1980). Randomization is done both to eliminate selection bias and to enable the proper use of statistical methods. Because randomization allocates subjects in an unbiased manner, potentially confounding variables tend to be equally distributed between experimental

Table 1. Assessment of reports of four clinical trials evaluating the efficacy of routine imaging ultrasound in pregnancy

Criteria	London 1982	Alesund 1984	Trondheim 1984	Glasgow 1984
Prior hypotheses	N	Y	Y	Y
Power calculation	N	N	Y	N
Eligibility criteria	U	Y	U	Y
Allocation	AN	RN	RN	AN
Withdrawals	N	N	N	Y
Description of regimen	Y	Y	Y	Y
Adherence to regimen				
Subjects	Y	Y	Y	Y
Doctors	N	Y	Y	Y
Blinding				
Subjects	Y	N	N	Y
Assessors	N	Y	Y	N
Unambiguous endpoints	Y,N	Y,N	Y,N	Y,N
Appropriate statistics				
Main effects	Y	Y	Y	Y
Subgroups	N	N	Y	N
Complications of screening	N	Y	Y	N

Y, yes; N, no, U, unclear, AN, alternate hospital numbers; RN, random numbers, sealed envelopes and control groups. Nevertheless, it is still useful to assess whether known risk factors were distributed equally between the study and control groups. This was attempted in all but the London trial.

Withdrawals

These were clearly retained within experimental and control groups in only the Glasgow trial, although the necessary data for the analysis of the outcome of primary interest were available in the published report of the Trondheim study. The unpublished records of the other trials provided similar data It is essential to retain the original randomly allocated groups for the primary analyses although additional analyses with clearly specified exclusions can be used for supplementary information (Chalmers *et al.* 1981). Excluding withdrawals, even those beyond the control of the investigation (e.g., spontaneous abortions), can vitiate the bias-eliminating effects of randomization (Mostellar *et al.* 1980). Any other analyses must be considered as supplementary or as hypotheses-generating exercises. Supplementary analyses are often useful, but the interpretation of such analyses must be conservative.

Study regimens

These were well described in each of the trials, and patient compliance with the regimen was uniformly high.

Adherence to the study regimen

This is crucial but often difficult to assess unless the investigators make careful efforts to document deviations from the protocol or even to design methods to quantify such deviations. The London study was seriously flawed by divulging ultrasound scan results to the doctors caring for 30% of the controls, and although technically this option was an acceptable part of the protocol, departure to such a degree from the original randomization makes data interpretation extremely difficult. Active efforts to assess medical adherence to the regimen were absent from the four trials. The appropriate use of ultrasound data by doctors, while technically not part of the protocols of any of these trials, is obviously a crucial aspect of any study. While explicit decision pathways based on scan results can be constructed, they were not done in these trials and intervention was ultimately based on clinical judgment While this may reflect the real world, one must recognize that trials of this type measure the effectiveness of a management practice rather than the potential efficacy of a procedure in an ideal setting. For example, in the Trondheim study, measurements of abdominal diameters were rarely used for diagnosis, despite evidence that they are more precise than the measures actually used (Bakketeig *et al.* 1984; Neilson *et al.* 1984).

Blinding of subjects and assessors

The conduct of management trials, such as those reported here, are subject to bias when either patients or those assessing outcomes are aware of the assignment of a patient to the experimental or control groups. Blinding (or masking) of patients was attempted in the British trials. Assessment of infant outcome was blinded in the Norwegian studies The British investigators relied on hospital records, a practice subject to observer bias in that doctors measuring and recording outcomes may know whether or not a scan had been done.

Unambiguous outcomes

When blinding is not possible, the use of the unambiguous outcomes such as death makes interpretation less subject to bias In these trials, outcomes were sometimes, as with perinatal death, unambiguous. Even in the case of a perinatal death, however, the attribution of cause of death, if important, could have been biased. A decrease in the rate of induction was the benefit most likely to be detected in these four trials. This outcome is, of course, easily quantified, yet, the indications for induction are variable and the attribution of indication for induction is potentially subject to observer bias.

Statistical analysis

This remains a source of confusion to readers of the clinical literature. Clear presentation of the simple distribution of results in both experimental and control groups is essential but is nevertheless sometimes overlooked by journals and authors. Comparative analyses and tests of statistical significance should be presented for the major endpoints, with a clear indication of the statistical tests used. Ideally, results should be presented as relative risks or risk differences with appropriate confidence intervals (Rothman 1978). *Post-hoc* analysis of subgroups on hypotheses inspired by looking at the results (data dredging) should generally not use conventional tests of statistical significance All the trials of routine ultrasound used appropriate statistics to assess main effects. None, however, calculated confidence intervals, and only the Trondheim authors demonstrated an understanding of the distinction between hypothesis testing (of the prior hypotheses) and data dredging to generate new hypotheses and to find supporting data for testing the major hypotheses.

Complications

While none of the trials was designed to assess the complications of routine ultrasound scanning, investigators should not fail to use these studies to look for potential adverse effects of a procedure. For example, three of the studies looked at maternal hospitalization as an indication of possible side-effects

Assessing reports of clinical trials

If one were limited to published data, much less could be said about the quality and comparability of the four trials. To demonstrate this point the four trials were assessed quantitatively, using a previously standardized method for evaluating trials (Chalmers *et al.* 1981) This system was modified slightly for the assessment of ultrasound screening trials. A score of over 80% is considered good while a report is occasionally rated at over 90%. In scoring the trials *only published data were used* The Trondheim publication scored highest for overall quality (68%), followed by the Glasgow (58%), London (38%) and Alesund trials (24%). With additional information that was not published each trial would have scored higher, especially the Alesund study which has only been published as a letter to the editor. The purpose of this exercise, however, was not to rate the four studies, but rather to emphasize the importance of adequate reporting of both methods and results. In this instance, the published literature leaves the reader with serious concerns about the quality of the largest trial (Alesund) and the only one to demonstrate benefit of routine ultrasound.

Results

Individual trials

The primary outcome of interest in all the trials was the effect of screening on rates of induction of labour. Previous observational studies had demonstrated that imaging ultrasound predicted the date of spontaneous onset of labour more accurately than did maternal history (Wladimiroff *et al.* 1978; Neilson *et al.* 1980). It was felt that because of more accurate dating of pregnancy. screening would reduce unnecessary induction done for supposed postmature pregnancy as well as decrease perinatal deaths and neonatal morbidity Maternal hospitalization was reported in response to a concern about increased hospital stay related to the use of ultrasound. Other findings resulting from *post-hoc* data analysis (data dredging) will not be discussed.

In three of the four trials, induction rates were lower in the ultrasound group although the differences were statistically significant in only the Alesund trial (Table 2). The duration of maternal hospitalization was lower in the experimental group in Alesund, higher in the experimental group in Trondheim and similar in both trial groups in the Glasgow trial. The rate of perinatal death was higher in the Alesund controls, but the difference was not statistically significant. Low Apgar scores were more frequent in the experimental group in all the trials but the difference never attained statistical significance. In the two trials for which data are available, the number of babies admitted for neonatal special care was greater in the control than in the experimental group, although the reverse was true when the total number of days spent in special care was considered.

Pooled analyses

In order to use trial data more efficiently, several studies of the same intervention can be pooled (Collins *et al.* 1985). This is particularly useful when trials are too small to detect real and potentially important effects of the intervention. There are, however, limitations of such pooling and one must be cautious in the interpretation of pooled analyses (Goldman & Feinstein 1979). Because of the breach in the screening regimen,

Table 2. Results of four clinical trials assessing the efficacy of routine imaging ultrasound in pregnancy

Characteristics	London 1982** Experimental	London 1982** Control	Alesund 1984 Experimental	Alesund 1984 Control	Trondheim 1984 Experimental	Trondheim 1984 Control	Glasgow 1984 Experimental	Glasgow 1984 Control
No of subjects	836	785	809	819	510	499	433	444
Scanning regimen	1-stage		2-stage		2-stage		2-stage	
Gestation at scan (weeks)	16		18,32		19,32		24,35–36	
No of subject hospitalized	NA	NA	184	269	104	58	43	46
Mean stay (days)	NA	NA	4·5	3·1	7·9	5·9	10·0	8·7
No induced (%)	104 (19·0)	107 (19·6)	15 (1·9)	64 (7·8)	32 (6·5)	38 (7·9)	129 (31·0)	129 (29·0)
Perinatal deaths *n* (rate/1000)	8 (10·2)	7 (9·5)	3 (3·7)	8 (9·8)	5 (9·8)	5 (10·0)	0 (0·0)	1 (2·3)
1-min Apgar score ≤7*								
No.	172	142	41	35	34	23	71	70
%	22·5	19.9	5·1	4·3	6·0	4·9	16·4	15·8
Neonatal intensive care								
Admissions	NA	NA	63	66	21	25	NA	NA
Mean stay (days)	NA	NA	12·0	10·7	25·3	18·7	NA	NA

NA, Data not available.

* Singleton births only.

** Data were available for later pregnancies not reported previously; data on induction only available for 1062 pregnancies.

the London trial has not been included in the pooled analyses presented here. Pooling is not appropriate in circumstances in which results vary widely, and the heterogeneity test gives a quantitative measure of the extent of variability in outcome among the trials (Collins *et al* 1985). Due to the variable effects of screening on the rates of induction, for example, pooling of these data from the three other trials could be done (χ^2 for heterogeneity = 23·5, $P<0·05$).

There is no statistical reason for not pooling mortality and Apgar-score data from the three trials (χ^2 for heterogeneity not significant, $P<0·05$) (Table 3). The pooled relative risk for

Table 3. Pooled results of three controlled trials assessing the efficacy of routine imaging ultrasound in pregnancy

Trial	Apgar score ≤7 at 1 min Experimental	Apgar score ≤7 at 1 min Control	Apgar score ≤7 at 1 min Variance	Perinatal deaths Experimental	Perinatal deaths Control	Perinatal deaths Variance
Alesund	41	35	18·11	3	8	2·73
Trondheim	34	23	13·42	5	5	2·48
Glasgow	71	70	29·61	0	1	0·25
TOTAL	146	128	61·12	10	14	5·46

	Pooled relative risk	95% confidence interval	Test for heterogeneity
Perinatal death	0·63	0·27, 1·47	χ^2_2 1·14 (NS)
Apgar score	1·16	0·91, 1·41	χ^2_2 1·06 (NS)

perinatal death was 0·63, indicating a 37% reduction in death associated with the routine use of ultrasound. This difference, however, was not statistically significant (CI = 0·27–1·47). A small increase in the rate of low Apgar scores was associated with routine ultrasound, but this difference was not statistically significant (RR = 1·16, CI = 0·91–1·41).

Discussion and conclusions

The purpose of this review was to assess systematically the results of four published trials which had been mounted to assess the routine use of imaging ultrasound in pregnancy. Most of the 14 criteria for assessment listed in Table 1 are either self-explanatory or have been described adequately above. There are, however, two concepts that require further elaboration: prior hypotheses and statistical power.

Tests of statistical significance are designed to measure the probability that an event may have occurred by chance. If a study is designed to test a specific hypothesis, a standard statistical measure (eg: χ^2 or a t-test) may show that the probability of a particular result occurring by chance is less than 1 in 20 ($P<0{\cdot}05$) if the null hypothesis is true. But on reviewing the data, other relations may be observed and application of the same statistical test to these relations may yield a value of $P<0{\cdot}05$. While not incorrect, this result cannot be interpreted in the same way as the test on the initial hypothesis. In a related area the probability that at least one statistically significant association will arise increases with the frequency of testing, and the true probability that such an association arises by chance is no longer less than 1 in 20. It has been shown that the effect of looking at four such hypotheses generated from multiple looks at the data effectively increases P to 0·19 rather than 0 05 (Ingelfinger *et al.* 1983). This is not to say, however, that looking at the data is not important. Such data dredging will uncover unsuspected associations which may both support the primary analyses or generate new hypotheses. Nevertheless, one must be careful to distinguish between the testing of *a priori* hypotheses and the generation of new hypotheses *post hoc.*

The statistical power of a trial is a measure of the probability that a true difference between populations will be detected. The calculation of sample size takes into account the prevalence of the outcome of interest (e.g., an induction rate of 10%), the expected change in the prevalence of the outcome due to the intervention under study (e.g , a 50% reduction in induced labours), and the level of statistical significance that is desired (e.g., $P<0{\cdot}05$) (Ingelfinger *et al* 1983). A study with a power of 80% will find a true difference to be statistically significant in eight of 10 trials conducted under comparable conditions. In the ultrasound trials, the inability to detect certain outcomes of interest should have been apparent prior to data collection. The Trondheim trial sample was based on a calculation that was designed to detect a 50% decrease in post-term induction. A 25% decrease would require a larger sample to have the same power. Similarly, a 50% decrease in perinatal mortality from 10/1000 to 5/1000 would require a sample size of over 10 000 pregnancies

The use of imaging ultrasound for specific clinical indications is widespread (*Lancet* 1984). Routine use of this procedure has been advocated for all pregnancies (Warsof *et al.* 1983) The apparent safety of ultrasound for both mother and fetus has encouraged its more extensive application, although concern about possible unrecognized long-term effects has been expressed by both professionals and lay organizations (NIH Consensus Development Conference 1984; Squire 1984).

Based on the evidence from the four clinical trials, what can one conclude about the efficacy of routine imaging ultrasound in pregnancy? The decrease in the rate of induction due to inappropriate classification of gestational age will be 'diluted' by induction for unrelated indications. Hence, the suggestion from the data that ultrasound screening does actually decrease the rate of induction is that much more striking. Yet, because this conclusion depends almost entirely on a single trial, one must be cautious before extrapolating beyond that particular study Caution is particularly indicated since there was no statistically significant reduction in perinatal morbidity and mortality associated with the routine use of ultrasound

In a similar situation, six controlled trials conducted over a decade failed to demonstrate any advantage of intrapartum fetal heart rate monitoring compared with intermittent auscultation. *Post hoc* examination of pooled data from these relatively small studies, however, suggested a possible benefit of intrapartum fetal heart rate monitoring and fetal acid–base assessment in the reduction of neonatal seizures (Chalmers 1979). A randomized controlled trial was then conducted to test this *a priori* hypothesis in over 13 000 women and confirmed this postulated effect of the use of electronic fetal monitoring and fetal acid–base assessment (Macdonald *et al.* 1985).

Given the uncertainty of the results of the four clinical trials designed to assess the efficacy of routine ultrasound in pregnancy, it is appropriate to conduct further, larger randomized controlled trials to test the following hypotheses Two-stage imaging ultrasound: (a) reduces the rate of unnecessary induction for improperly classified postdate pregnancies; (b) decreases neonatal morbidity as measured by the 1-min Apgar score or admission for neonatal intensive care; (c) decreases perinatal mortality.

The sample sizes for such trials should be calculated for the least common outcome, in this instance perinatal mortality. If, for example, one wished to detect a 50% decrease in the perinatal death rate from 10 per 1000 to 5 per 1000 with a power of 90% at a 5% level of significance, the study would require 6250 women in both the experimental and control groups. This sample would then also be adequate for the more common outcomes, unnecessary induction and neonatal morbidity.

While designed to assess the efficacy of routine imaging ultrasound, the proposed trial could also be used in an exploratory manner to define better any long-term adverse effects possibly associated with routine ultrasound.

It is of interest that in 1973 a trial very similar to the one proposed here was piloted successfully but then rejected by the Medical Research Council (Mole 1984). Instead, the rapid and widespread diffusion of ultrasound into medical practice has preceded the publication of the trials reviewed here. This premature use of new technology pervades modern medical practice. Obstetrics, like the rest of medicine, must adopt a sensible but rigorous approach to the evaluation of new technology. This is particularly true of procedures intended for routine use in large populations. In such circumstances properly conducted randomized controlled trials of adequate size will provide the best data for both clinical and public health policy.

Finally, it is not enough to determine that a screening procedure is efficacious, the human and monetary costs of the procedure must also be assessed, and the effectiveness, safety and acceptability of subsequent interventions must be considered. Even if routine use of ultrasound successfully detects serious congenital malformations, is the intervention, elective abortion, acceptable and legally available to the individual involved? Monetary cost is another important factor. Any procedure used in essentially all pregnancies will have large direct financial costs In addition, one must recognize those costs with no direct monetary equivalents such as the loss of a woman's time and any anxiety arising from false-positive test results. Before a rational decision can be made about the appropriate use of this technology the value of ultrasound screening must be compared to that of other activities in obstetrical practice designed to reduce unnecessary induction and to decrease perinatal morbidity and mortality.

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The extent and antecedents of uncertain gestation

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Summary. The extent and genesis of uncertainty of gestation has been studied in a total obstetric population, using in all cases a best clinical estimate of gestation made according to a specific protocol. In 73·2% of patients, the estimate was assessed as certain, in 19·7% as approximate, and in 7·1% as uncertain. Uncertainty assessed in this way has several antecedents, and coding of only one of these (presence or absence of a precise date for the last menstrual period) is insufficient in data to be used for research in which gestation length is to be used as a variable.

Much perinatal morbidity and mortality is associated with short gestation at birth and with low birthweight for gestation. Optimal obstetric management of these conditions requires a reliable estimate of gestation. Unfortunately this is often not available because of uncertainty about the date of the last menstrual period (LMP), irregular menstrual cycles, oral contraceptive use or discrepancies between the clinical findings and the history.

Because the estimate of gestation is so important for the successful management and outcome of pregnancy, routine ultrasonic scanning in early pregnancy is common but, even where this is the practice, some uncertainty must remain because of machine and observer errors. Moreover, some women (22% in this study) present at hospital clinics after 20 weeks gestation, when ultrasonic scanning measurements correlate less well with gestational age because of variations in growth.

In research studies of problems concerning gestation (e.g the management of preterm labour, or the analysis of the factors affecting perinatal mortality), it is common practice to exclude cases where gestation is uncertain. The criteria used in defining uncertain gestation are, however, rarely specified. Thomson *et al.* (1968) did give an account of their procedure for estimating gestation, but felt obliged to exclude as many as 10% of women because of insufficient or contradictory information. This is no longer so necessary because of the availability of information from ultrasonic scans and paediatric maturity scores.

The purpose of this paper is to quantify the extent and nature of the potential problem posed by uncertain dates, irregular menstruation and oral contraceptive use, and to describe a system of classification of the extent of uncertainty of gestation.

Subjects and methods

The data were drawn from the Aberdeen Maternity and Neonatal Data Bank (Samphier 1980; Samphier & Thompson 1981) which contains extensive information on all gynaecological and obstetric events in Aberdeen since 1948. The population for this analysis consisted of 11 602 women giving birth to babies in Aberdeen City District from 1976 to 1980, since detailed coding of certain items relevant to gestation began in 1976.

Data available on the sociodemographic characteristics of the mother include social class, defined in terms of her husband or partner's

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occupation, or her own occupation if single, age, civil status of the child, education (recorded only for primiparae), smoking habit and parity.

Gestation length is conventionally calculated as the interval between the first day of the last menstrual period (LMP) and the day of delivery. Similarly the expected date of delivery is calculated as 280 days or 40 weeks from the first day of the LMP. Either calculation makes the assumption that ovulation (and conception) occurs 14 days after that date. This assumption is invalid and inappropriate when the menstrual cycle is prolonged or irregular (since ovulation then occurs about 14 days before the *next* expected menstrual period), if the LMP is an oral contraceptive withdrawal bleed (as there may be post-pill amenorrhoea), if the LMP is abnormal (as the last bleeding may then be a threatened abortion rather than a true period), or if the woman is not sure about the date of the LMP.

In Aberdeen, the woman's statement about the date of the LMP, its nature and certainty (recorded as certain, approximate or uncertain), the menstrual cycle and recent contraceptive use are recorded on a structured case record designed by a sub-committee of the Scottish Executive of the Royal College of Obstetricians and Gynaecologists. Specially trained clerical staff extract all these details onto a coding sheet, together with the characteristics of the mother and the progress and outcome of her pregnancy.

Where the LMP is stated as certain, the cycle is regular, there is no recent oral contraceptive use and no doubt about the gestation is mentioned in the case record, the coding staff calculate the gestation length in completed weeks in the conventional way from the LMP and code the estimate of gestation as certain. All other cases must be referred by the coding staff to two experienced obstetricians (M.H.H. and D.M.C.). Criteria for this referral are specified in Appendix 1.

The obstetricians follow an agreed protocol (detailed in Appendix 2) in which certain menstrual data, in the absence of oral contraptive use, take precedence over other conflicting observations, unless at least two of these corroborate each other Corroborated evidence takes precedence over uncorroborated. Thus a best clinical estimate of gestation based *usually* upon certain menstrual dates, but in a substantial minority upon other evidence, is made for every pregnancy, and the certainty of this estimate categorized as certain, approximate or uncertain. The assignment of a value for the gestation length and the categorization of certainty is done 'blind' in the course of routine coding so that it can be used for research studies.

Results

The application of the protocol described above resulted in 8497 (73%) being assessed as certain gestation, 2286 (20%) as approximate, and 819 (7%) as uncertain. A number of factors are involved in the genesis or resolution of this uncertainty; uncertainty of the date of the LMP, irregular menstruation and oral contraceptive use tend to cause uncertainty and the employment of scans and X-rays to reduce it.

No date for LMP was coded in 101 pregnancies (1%). The reasons are detailed in Table 1. These have been included in subsequent tables as 'uncertain LMP'.

Table 1. Reasons for absence of information about the LMP

Reason	No
No period since previous abortion/birth	32
Prolonged amenorrhoea	20
Conceived during oral contraceptive use	16
Continual bleeding throughout pregnancy	1
Concealed pregnancy or no information	32
Total	101

Where a date was given for the LMP it was recorded in the case sheet as certain in 9054 (78%) as approximate in 1523 (13%) and as uncertain in 924 (8%).

Women whose LMP was recorded as uncertain were much less likely (only 50%) to book for antenatal care before 20 weeks than those with an approximate or certain LMP (71 and 83% respectively).

Women with an uncertain LMP were, of course, more likely to have an ultrasonic scan or a maturity X-ray than those with an approximate or certain LMP.

Table 2 shows that the characteristics of the women with uncertain LMP were generally more unfavourable than those with approximate or certain LMP (more women in social class IV and V or not classified, more teenage mothers, more illegitimate births, more with minimum education, more smokers, and more women of higher parity).

Table 2. Maternal characteristics by recorded certainty of date of last menstrual period (LMP)

	Certainty of date of LMP							
	Certain		Approximate		Uncertain		Total	
Characteristic	No	%	No	%	No.	%	No	%
Social class								
I–IIINM	3140	34·7	356	23·4	178	17·4	3674	31·7
IIIM	3149	34·8	563	37·0	354	34·5	4066	35·0
IV–V	2314	25·6	509	33·4	370	36·1	3193	27·5
No information	451	4·9	95	6·2	123	12·0	669	5·8
Total	9054	100·0	1523	100·0	1025	100·0	11602	100·0
Age (years)								
14–19	722	8·0	306	20·1	301	29·4	1329	11·4
20–29	6601	72·9	991	65·1	618	60·3	8210	70·8
30+	1731	19·1	226	14·8	106	10·3	2063	17·8
Total	9054	100·0	1523	100·0	1025	100·0	11602	100·0
Child's civil status								
Legitimate	8393	92·7	1244	81·7	683	66·6	10320	89·0
Illegitimate	661	7·3	279	18·3	342	33·3	1282	11·0
Total	9054	100·0	1523	100·0	1025	100·0	11602	100·0
Education of primiparae								
Minimum	1902	52·4	464	66·8	343	78·0	2709	56·9
More	1725	47·6	231	33·2	97	22·0	2053	43·1
Total	3627	100·0	695	100·0	440	100·0	4762	100·0
Smoking (cigarettes/day)								
0	5302	58·6	686	45·0	409	39·9	6397	55·1
1–10	1322	14·6	267	17·5	200	19·5	1789	15·4
11+	2430	26·8	570	37·5	416	40·6	3416	29·5
Total	9054	100·0	1523	100·0	1025	100·0	11602	100·0
Parity								
0	3958	43·7	753	49·4	512	49·9	5223	45·0
1–2	4762	52·6	709	46·5	447	43·6	5918	51·0
3+	334	3·7	61	4·0	66	6·5	461	4·0
Total	9054	100·0	1523	100·0	1025	100·0	11602	100·0

Table 3 summarizes the antecedents of certainty and uncertainty of gestation. There is a relation between uncertainty of LMP as recorded on the case sheet and uncertainty of gestation as coded after reviewing all available information, but there is not complete correspondence. For example, in 1169 women (13%) with certain LMP other corroborated information conflicted with this and the gestation is, therefore, quoted as uncertain or approximate. On the other hand, two women had an uncertain date of LMP but the gestation was coded as certain as the date of ovulation induction with gonadotrophins was known. Unrecorded or long menstrual cycles are a factor in uncertainty of gestation, but only in a small minority of cases Oral contraceptive use before conception was more important. This was recorded in 11% of women overall, but in as many as 45% of those whose gestation was assessed as approximate. Such women usually had a scan at booking because of this history, thus clarifying the assessment of gestation.

The use of biophysical measurements such as ultrasonic scanning helped to resolve uncertainty of gestation to a limited extent. Scanning was recored most frequently amongst those coded as having approximate gestation and least frequently when gestation was assessed as certain. Maturity X-rays on the other hand were

Table 3. Antecedents of certainty/uncertainty of gestation

	Certainty of gestation							
	Certain		Approximate		Uncertain		Total	
Antecedent factors	No	%	No	%	No	%	No	%
Menstrual cycle (days)								
Not stated	100	1 2	57	2·5	47	5·7	204	1·8
1–35	7711	90·7	1861	81·4	637	77·8	10209	88·0
36–98	495	5·8	190	8·3	71	8·7	756	6·5
Irregular	191	2·3	178	7·8	64	7 8	433	3·7
Pill withdrawal bleed								
Yes	141	1 7	1020	44·6	118	14·4	1279	11·0
No	7611	89·6	1090	47·7	564	68·8	9265	79·9
No information	745	8·7	176	7 7	137	16·8	1058	9·1
Sonar scan								
Yes	3280	38·6	1656	72·4	487	59·5	5423	46 7
No	5217	61·4	630	27·6	332	40·5	6179	53·3
Maturity X-ray								
Yes	454	5·3	215	9·4	88	10·7	757	6·5
No	8043	94·7	2071	90·6	731	89·3	10845	93·5
Certainty of date of LMP								
Certain	7885	92·8	1026	44·9	143	17 5	9054	78 0
Approximate	610	7 2	673	29 4	240	29·3	1523	13·1
Uncertain	2*	0·0	587	25·7	436	53·2	1025	8·9
Totals	8497	100·0	2286	100·0	819	100·0	11602	100·0

*Ovulation induced pregnancies.

rather more likely to be performed in women ultimately coded as uncertain gestation (usually those who had booked too late for a reliable ultrasonic scan).

It is important to quantify the possible discrepancies that may arise between the best clinical estimate described above and an estimate based solely upon time elapsed since the LMP

The discrepancies between the best clinical estimate of gestation and the gestation as calculated from the LMP are shown in Fig. 1 analysed by certainty of the date of the LMP and in Fig. 2 analysed by irregular cycle and oral contraceptive use. A positive value on the horizontal axis means that the gestation calculated from the LMP was greater than the best clinical estimate of gestation, whilst a negative value means that it was less.

Fig. 1 shows that the discrepancies are considerably greater among pregnancies with uncertain LMP than when it is certain; thus, of those with an uncertain LMP, 20% have a negative discrepancy of ≥1 week and 28% a positive discrepancy of ≥1 week, as against 4% and 5% of certain LMPs respectively Fig. 2 shows that the discrepancies are usually such that the best clinical estimate of gestation for women who have experienced a long cycle or who have used oral contraceptives is larger than the estimate of gestation derived from the LMP Indeed, in a substantial minority there were discrepancies of ≥3 weeks; primarily amongst those with uncertain dates of LMP, but also amongst those with long cycles or oral contraceptive use.

To summarize, gestation length calculated from the LMP alone will tend to be an overestimate and rates of preterm delivery will be underestimated.

Discussion

Uncertainty of gestation is an everyday problem for the clinician who in normal practice, on the basis of all the available information, has to

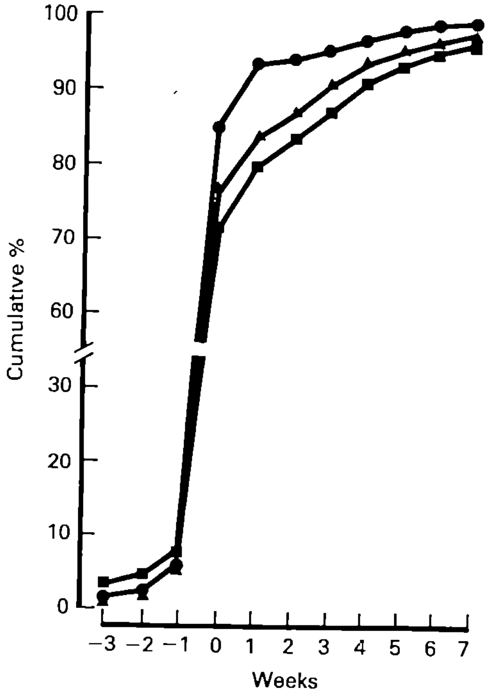

Fig. 1. Discrepancy in weeks between the best clinical estimate and gestation calculated from the last menstrual period (LMP) LMP ● certain; ▲ approximate, ■ uncertain.

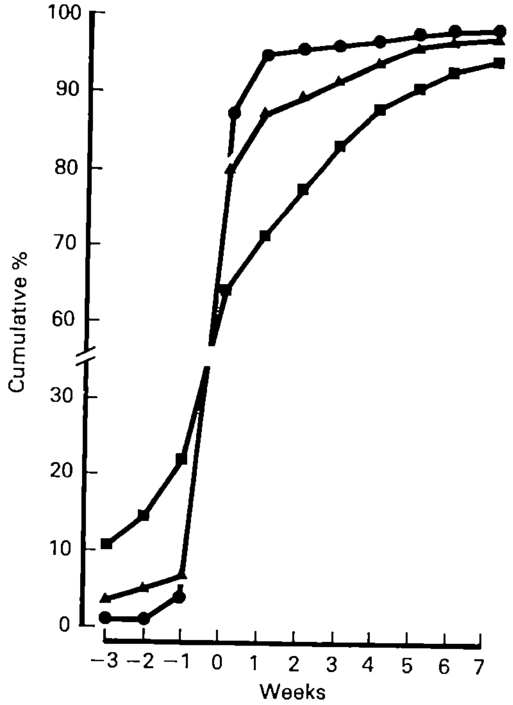

Fig. 2. Discrepancy in weeks between the best clinical estimate and gestation calculated from the LMP by the cycle length and oral contraceptive use ● All cases, ▲ cycle >35 days, ■ LMP pill withdrawal

make both an estimate of the gestational age and a judgment as to the reliability of that estimate in order to manage the pregnancy whether at the antepartum or intrapartum stage

The problem of uncertain gestation is often ignored in research studies. The calculation of gestation length from LMP alone gives rise to obvious nonsense such as the reporting by Hoffman *et al.* (1974) of birthweights of >1000 g at less than 20 weeks gestation and of gestation up to 52 weeks. Frequently the pursuit of perfection has led to the blanket use of a particular criterion or set of criteria for gestational age (e.g. crown–rump length (CRL), biparietal diameter (BPD) (Adam & Robinson 1980), Dubowitz scores (Roberts *et al.* 1979), or even the actual date of delivery (Brindle 1981)). Each of these criteria has its own problems. The use of CRL and BPD depend upon women attending for antenatal care early enough, which happens less often among women at risk of poor pregnancy outcome, and the estimate of gestation is influenced by fetal size. Dubowitz scores are relatively accurate in preterm babies but, at term, when most babies are born, are accurate only to within 2 weeks (Dubowitz *et al* 1970). But the main problems with using any of these criteria in place of menstrual data is that they were all originally validated using a series of women with certain or 'immaculate' dates.

In these circumstances it is clearly illogical to claim that such criteria should take precedence over certain menstrual data where these exist. Further, when compared to the original research studies, the accuracy of the tests in routine clinical practice will be affected by factors such as the gestation at booking (especially when deciding the weight to be placed upon the result of a scan) and, in general, by local staff expertise. Moreover, the criteria may conflict with each other

For epidemiological research, there is a further disadvantage in relying upon one criterion or a particular group of criteria in that it then becomes impossible to assign a gestation to those women for whom results are not available Uncertainty of gestation has multiple antecedents but at least one (ignorance of or uncertainty of the LMP) is strongly associated with unfavourable characteristics both in our study and that of Buekens *et al.* (1984). Whilst this may be partly due to the 'attribution of incompetence' described by Macintyre (1978) this seems unlikely to be the only explanation.

We should note that the considerable extent of uncertainty of gestation revealed in this research study is, of course, less than that routinely observed in clinical practice during pregnancy since we have used data such as paediatric maturity scores that are not available to obstetricians making antepartum or intrapartum decisions. Secondly, although pregnancies with certain LMP are very likely to be assessed as being of certain gestation, even after the pregnancy is completed, the correlation of other criteria of gestation with certainty of LMP is less than might be expected. For this reason routine coding of the date and certainty of the LMP alone is insufficient for research purposes.

We would agree with Buekens *et al.* (1984) that exclusion of women with an unknown LMP will introduce bias but 'unknown LMP' is quite inadequate as a definition of uncertain gestation. Ideally we would argue that for research studies, a best clinical estimate of gestation should be made for all pregnancies according to an agreed consistent protocol and preferably done 'blind' by a clinician not involved in the research. There are advantages in having three categories of uncertainty (certain, approximate and uncertain) so that the 'certain' category may be considered alone when gestation is central to the research (e.g. in the construction of birthweight for gestation tables), but the 'approximate' cases may also be included, and perhaps the 'uncertain' cases also, when considering subjects such as preterm labour or pregnancy complications at different gestation. The implications of excluding some sections of the population from research studies have been explored elsewhere (Hall & Carr-Hill 1985).

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Appendix 1

Case notes to be scrutinized by medical staff for gestation estimation

1. Expected date of delivery (EDD) changed by ⩾1 week, or not specified exactly, on case sheet.
2. Date of last menstrual period (LMP) approximate or uncertain.
3. LMP abnormal (short, long, late or early).
4. Menstrual cycle ⩾35 days.
5. LMP is pill withdrawal bleed.
6. LMP occurs within 4 weeks after date of stopping oral contraceptive, or before stopping oral contraceptive.
7. First-visit uterine size differs from dates by ⩾2 weeks (look at vaginal examination findings).

8. Doubtful gestation as special feature.
9. Other serious doubts about gestation (e.g. in discharge summary).

Appendix 2.

Aberdeen Maternity Hospital 1976. Criteria to be followed in clinical gestation estimation

Gestation will be calculated as completed weeks following the first day of the last menstrual period. Three codes are available:

a) Certain (taken to mean certain to within ±1 week).
b) Approximate (taken to mean certain to within ±2 weeks).
c) Uncertain (taken to mean certain to within ±4 weeks).

1. LMP certain

Where the date of the last menstrual period (LMP) (even if abnormal) is given as *certain* (but excluding cases where the last menstrual period is a pill withdrawal bleed, or where the menstrual cycle is every 36 days or more). The gestation will be calculated from the last menstrual period (and coded as certain) unless any of the following estimates of gestation differs from that calculation by 4 weeks or more.

a) Vaginal examination at less than 20 weeks.
b) X-ray at 36 weeks or over (X-rays reported as <36 weeks should be taken to mean only that the gestation is <36 weeks).
c) Ultrasonic scan at 30 weeks or less.
d) Maturity score (Dubowitz).
e) Maturity amniocentesis.

In the event of such a discrepancy, the conflicting evidence should be taken as correct only if corroborated by a second piece of evidence. The gestation should then be coded as approximate (at best).

2. LMP approximate

Where the date of the last menstrual period is given as approximate, the gestation may be coded as certain if corroborated by other evidence, but as approximate if uncorroborated.

3. LMP uncertain

Where the date of the last menstrual period is given as uncertain, but corroborative evidence, e.g., scan available, the coding may be as approximate; but as uncertain if uncorroborated.

4. Menstrual cycle long

Where the menstrual cycle is ≥36 days but regular, the gestation will be calculated assuming a luteal phase of 2 weeks, but coded as approximate.

Where the cycle is ≥36 days but irregular, and other evidence available (as in 1), the gestation should be calculated according to the other evidence and coded as approximate (at best). If no other evidence is available, code as uncertain.

5. LMP pill withdrawal bleed

If the last menstrual period is a pill withdrawal bleed, but other evidence available, the gestation should be calculated from the other evidence and coded as approximate (at best).

If no other evidence is available, the gestation should be calculated from the last menstrual period but coded as uncertain. In all cases on oral contraception in early pregnancy LMP will be coded as a withdrawal bleed.

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The significance of uncertain gestation for obstetric outcome

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Summary. An analysis of 11 454 singleton births in a 'total obstetric population' (Aberdeen City District) from 1976 to 1980 showed that women whose gestation was assessed as approximate or uncertain had less favourable characteristics than the certain group. Uncertainty was significantly related to adverse pregnancy outcomes such as perinatal mortality, low birthweight, and spontaneous preterm delivery, and the association with the adverse outcomes was independent of unfavourable maternal characteristics. Moreover, uncertainty 'explained' adverse outcomes better than the traditional sociodemographic variables used in the analysis. It is argued that research findings based only on women of certain gestation cannot be generalized to total populations including women of uncertain gestation and will be subject to bias.

The problems of bias in obstetric research because of uncertain or unknown gestational length may arise at several levels. Firstly, no information may be coded in some data sets. Hoffman *et al.* (1974) noted that in the USA in 1958 only some states *recorded* the date of the last menstrual period (LMP) and the proportion doing so was less in the south and the north-east; it was less in non-metropolitan counties in the west, but in metropolitan counties in the south and north-east, among births to black women, it was less often recorded in non-metropolitan counties.

Seondly, a substantial minority of women (even in developed countries) may not know the date of their LMP, and those women may have different characteristics from women who do. Hoffman *et al.* (1974) found that in the counties where LMP was coded, no data were available on the birth certificates of 19% of births to white women and 25% of births to black women. In hospital data from Belgium, Buekens *et al.* (1984) found that 16% of women did not know the date of the LMP, but amongst them, teenagers, North Africans, single women, illiterate women and working class women were over-represented. Ignorance of the LMP is, however, an inadequate measure of uncertainty of gestation, as we have argued elsewhere (Hall *et al.* 1985).

Next, adverse pregnancy outcome may be commoner in women of uncertain gestation. A higher proportion of babies with low birthweight in the women of unknown gestation is reported by Thomson *et al.* (1968) and Buekens *et al.* (1984) and both sets of authors speculate that this may be attributable to the poor socio-economic and sociodemographic status of the women concerned.

The purpose of this paper was to analyse, according to uncertainty of gestation, both the characteristics of the women and the outcome of the pregnancy, and to assess whether any adverse outcomes associated with uncertainty of gestation are actually attributable to any

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unfavourable characteristics of the women or are independent of them. This analysis has been performed in a total obstetric population for which a 'blind' best clinical estimate of gestation length and an assessment of the certainty of the estimate has been made for every woman.

Subjects and methods

This analysis was based on all 11 454 singleton births in Aberdeen City District from 1976 to 1980, excluding only those for whom no information was available for any particular variable. The assignment of a value for gestation length, the assessment of its certainty, and the recording of sociodemographic characteristics was as described in our earlier paper (Hall *et al.* 1985). The outcomes studied were perinatal mortality, low birthweight (<2500 g), preterm delivery (<37 weeks) in women with spontaneous onset of labour (those with induced labour were excluded, as induction rates are determined more by obstetric policies than by pathology) and mean birthweight in women delivered (a) at or after 37 weeks, (b) at less than 37 weeks.

The basic method of analysis was to examine

Table 1. Distribution of maternal characteristics by certainty of gestation

	Certainty of gestation											
	Certain			Approximate			Uncertain			Total		
Characteristic	No.	%	(%)‡	No	%	(%)	No	%	(%)	No.	%	(%)
Social class of married women*												
I–IIINM	2868	37·1	(81·4)	505	27·6	(14·3)	152	27·3	(4·3)	3525	34·9	(100 0)
IIIM	2783	36·0	(74·7)	731	39·9	(19·6)	213	38·3	(5·7)	3727	36·8	(100·0)
IV–V	2084	26·9	(72·6)	595	32·5	(20·7)	191	34·4	(6·7)	2870	28·4	(100·0)
Total	7735	100·0	(76·4)	1831	100·0	(18·1)	556	100·0	(5·5)	10122	100·0	(100·0)
Age (years)												
14–19	679	8·0	(51·9)	396	18·1	(30·3)	234	29·5	(17·8)	1309	11·4	(100·0)
20–29	6082	71·8	(75·0)	1551	70·9	(19·1)	473	59·7	(5·8)	8106	70·8	(100·0)
30+	1713	20·2	(84·1)	240	11·0	(11·8)	85	10·7	(4·2)	2038	17·8	(100·0)
Total	8474	100·0	(74·0)	2187	100·0	(19·1)	792	100·0	(6·9)	11453	100·0	(100·0)
Child's civil status												
Legitimate	7810	92·3	(76·8)	1812	82·9	(17·8)	551	69·7	(5·4)	10173	88·9	(100·0)
Illegitimate	651	7·7	(51·5)	373	17·1	(29·5)	240	30·3	(19·0)	1264	11·1	(100·0)
Total	8461	100·0	(74·0)	2185	100·0	(19·1)	791	100·0	(6·9)	11437	100·0	(100·0)
Education of primiparae												
Minimum	1783	52·8	(66·3)	668	66·1	(24·8)	239	72·2	(8·9)	2690	57·1	(100·0)
More	1591	47·2	(78·6)	342	33·9	(16·9)	92	27·8	(4·5)	2025	42·9	(100·0)
Total	3374	100·0	(71·6)	1010	100·0	(21·4)	331	100·0	(7·0)	4715	100·0	(100·0)
Smoking (cigarettes/day)												
0	4940	60·7	(78·2)	1028	49·0	(16·3)	347	45·2	(5·5)	6315	57·4	(100·0)
1–10	1252	15·4	(71·1)	364	17·3	(20·7)	146	19·0	(8·3)	1762	16·0	(100·0)
11+	1945	23·9	(66·5)	706	33·7	(24·1)	274	35·7	(9·4)	2925	26·6	(100·0)
Total	8137	100·0	(74·0)	2098	100·0	(19·1)	767	100·0	(7·0)	11002	100·0	(100·0)
Parity†												
0	3784	44·7	(71·7)	1096	50·1	(20·8)	396	50·0	(7 5)	5276	46·1	(100·0)
1–2	4382	51·7	(76·4)	1009	46·1	(17·6)	343	43·3	(6·0)	5734	50·1	(100·0)
3+	308	3·6	(69·4)	83	3·8	(18·7)	53	6·7	(11·9)	444	3·9	(100·0)
Total	8474	100·0	(74·0)	2188	100·0	(19·1)	792	100·0	(6·9)	11454	100·0	(100·0)

* IIINM refers to the non-manual group in the Registrar General's Class III, IIIM refers to the manual group
† Parity is defined as the number of completed viable pregnancies excluding the index pregnancy.
‡ Percentages in parentheses total in rows.

the outcomes in cells defined by categories of maternal characteristics and different levels of certainty of gestation. Since both maternal characteristics and uncertainty of gestation may be associated with adverse outcomes, but the interrelation may be complex, analysis of variance has been performed to clarify two points. (i) How does uncertainty of gestation interact with each of the maternal characteristics in turn in associations with reproductive outcome? (ii) When all documented maternal characteristics are analysed together, is there evidence that uncertainty of gestation is independently associated with reproductive outcome?

The procedures used were those in the Statistical Package for the Social Sciences (Hull & Nie 1981) in two corresponding modes; first, separate analyses of variance entering certainty of gestation together with each maternal characteristic in turn, allowing for the possibility of an interactive term; second, a multivariable analysis entering certainty of gestation with all the maternal characteristics, considering only the direct (or main) effect of each variable.

Because of the complexity of the results, we have reported in the text only whether or not variables were statistically significant at the 5% level.

Results

Maternal characteristics

Scrutiny of the column percentages in Table 1 shows the distributions of maternal characteristics by the degree of certainty of gestation. There was a clear gradient in the direction of maternal characteristics being more unfavourable (lower

Table 2. Perinatal mortality rate (PMR) by certainty of gestation and maternal characteristics

	Certainty of gestation							
	Certain		Approximate		Uncertain		Total	
Characteristic	Number	PMR	Number	PMR	Number	PMR	Number	PMR
Social class of married women								
I–IIINM	2868	7·3	505	9·9	152	39·0	3525	9·0
IIIM	2783	11·1	731	10·9	213	23·0	3727	11·8
IV–V	2084	8·2	595	15·1	191	20·0	2870	10·5
Total	7735	8·9	1831	12·0	556	27·0	10122	10·4
Age (years)								
14–19	679	13·3	396	15·2	234	12·8	1309	13·8
20–29	6082	9·3	1551	10·9	473	21·0	8106	10·4
30+	1713	8·2	240	20·8	85	58·8	2038	9·8
Total	8474	9·4	2187	13·3	792	22·7	11453	11·1
Child's civil status								
Legitimate	7810	8·8	1812	13·8	551	29·0	10173	10·8
Illegitimate	651	16·9	373	10·7	240	8·3	1264	13·4
Total	8461	9·5	2185	13·3	791	22·8	11437	11·1
Education of primiparae								
Minimum	1783	12·3	668	16·5	239	12·6	2690	13·3
More	1591	12·5	342	14·3	92	32·6	2025	13·8
Total	3374	12·4	1010	15·9	331	18·2	4715	13·5
Smoking (cigarettes/day)								
0	4940	7·7	1028	8·8	347	25·9	6315	8·9
1–10	1252	7·1	364	13·7	146	27·4	1762	10·2
11+	1945	14·3	706	17·0	274	14·6	2925	15·0
Total	8137	9·1	2098	12·4	767	22·2	11002	10·7
Parity								
0	3784	12·2	1096	15·5	396	20·2	5276	13·5
1–2	4382	7·1	1009	10·0	343	14·6	5734	8·0
3+	308	9·7	83	24·0	53	94·3	444	22·0
Total	8474	9·4	2188	13·3	792	22·7	11454	11·1

social class, more teenagers, more illegitimate births, less education, more smokers, more women of parity 3+) the more uncertain the gestation. The 'approximate' category usually lay in an intermediate position between 'certain' and 'uncertain'. Also, in Table 1 the row percentages show the distribution of uncertainty of gestation by maternal characteristics. Only just over half of the teenagers or of the single women were of certain gestation.

Pregnancy outcomes

Perinatal mortality. Firstly (Table 2), only 63% of the perinatal deaths occurred in the group with certain gestation. Next the perinatal mortality rate was higher the more uncertain the gestation, and the gradient with uncertainty was steeper than with most of the sociodemographic variables. Within individual categories of maternal characteristics, perinatal mortality still tended to increase with uncertainty of gestation,

Table 3. Low birthweight (LBW) by certainty of gestation and by maternal characteristics

	Certainty of gestation												Total			
	Certain				Approximate				Uncertain							
		LBW				LBW				LBW				LBW		
Characteristic	Total	*n*	%	(%)	Total	*n*	%	(%)	Total	*n*	%	(%)	Total	*n*	%	(%)
Social class of married women																
I–IIINM	2868	123	4·3		505	24	4·8		152	12	7·9		3525	154	4·5	
IIIM	2783	152	5·5		731	58	7·9		213	19	8·9		3727	229	6·1	
IV–V	2084	142	6·8		595	58	9·8		191	19	10·0		2870	219	7·6	
Total	7735	417	5·4	(68·7)*	1831	140	7·7	(23·1)	556	50	9·0	(8·2)	10122	607	6·0	(100·0)
Age (years)																
14–19	679	57	8·4		396	42	10·7		234	28	12·0		1309	127	9·7	
20–29	6082	346	5·7		1551	112	7·2		473	38	8·0		8106	498	6·1	
30+	1713	87	5·1		240	22	9·2		85	11	12·9		2038	118	5·8	
Total	8474	490	5·8	(65·9)	2187	176	8·1	(23·6)	792	77	9·7	(10·4)	11453	743	6·5	(100·0)
Child's civil status																
Legitimate	7810	415	5·3		18112	139	7·7		551	51	9·3		10173	605	6·0	
Illegitimate	651	75	11·5		373	37	9·9		240	26	10·8		1264	138	10·9	
Total	8461	490	5·8	(65·9)	2185	176	8·1	(23·6)	791	77	9·7	(10·4)	11437	743	6·5	(100·0)
Education of primiparae																
Minimum	1783	151	8·5		668	68	10·2		239	21	8·8		2690	240	8·9	
More	1591	82	5·2		342	27	7·9		92	8	8·7		2025	117	5·8	
Total	3374	233	6·9	(65·3)	1010	95	9·4	(26·6)	331	29	8·8	(8·1)	4715	357	7·6	(100·0)
Smoking (cigarettes/day)																
0	4940	195	4·0		1028	51	5·0		347	32	9·2		6315	278	4·4	
1–10	1252	91	7·3		364	42	11·5		146	16	11·0		1762	149	8·5	
11+	1945	191	9·8		706	81	11·5		274	28	10·2		2925	300	10·3	
Total	8137	477	5·9	(65·6)	2098	174	8·3	(23·9)	767	76	9·9	(10·5)	11002	727	6·6	(100·0)
Parity																
0	3784	270	7·1		1096	107	9·8		396	40	10·1		5276	417	7·9	
1–2	4382	201	4·6		1009	62	6·1		343	29	8·5		5734	292	5·1	
3+	308	19	6·2		83	7	8·4		53	8	15·1		444	34	7·7	
Total	8474	490	5·8	(65·9)	2188	176	8·0	(23·7)	792	77	9·7	(10·4)	11454	743	6·5	(100·0)

* Percentages in parentheses total in rows

with the exception of some rows with rather small numbers (teenagers, single women, primiparae with least education, and those smoking ≥11 cigarettes per day). The analysis of variance (Table 7) showed that the gradient with uncertainty was statistically highly significant (except in the category of education of primiparae) but the maternal characteristics did *not* have a statistically significant effect upon perinatal mortality except in conjunction with uncertainty of gestation. Uncertainty of gestation was the only variable which was statistically significant when all characteristics were considered together (Column 1, Table 8).

Low birthweight. Only 66% of low-birthweight babies were born to mothers with certain gestation (Table 3). Low birthweight was more common in the uncertain gestation group (10%) than in the certain gestation group (6%) and again the gradient with uncertainty was steeper than with any maternal characteristic except smoking habit. Within each separate category of maternal characteristic, the tendency for the low-birthweight rate to increase with uncertainty of gestation persisted except where numbers were very small. The analysis of variance (Table 7) showed that both the gradients with uncertainty and with maternal characteristics were highly

Table 4. 'Spontaneous' preterm delivery (SPD) by certainty of gestation and maternal characteristics

	Certainty of gestation											
	Certain			Approximate			Uncertain			Total		
		SPD			SPD			SPD			SPD	
Characteristic	Total	*n*	%	Total	*n*	%	Total	*n*	%	Total	*n*	%
Social class of married women												
I–IIINM	2868	93	3·2	505	16	3·2	152	5	3·3	3525	114	3·2
IIIM	2783	90	3·2	731	35	4·8	213	19	8·9	3727	144	4·9
IV–V	2084	82	3·9	595	36	6·1	191	14	7·3	2870	132	4·6
Total	7735	265	3·4	1831	87	4·8	556	38	6·8	10122	390	3·9
Age (years)												
14–19	679	35	5·2	396	36	9·1	234	31	13·2	1309	102	7·8
20–29	6082	211	3·5	1551	69	4·4	473	31	6·6	8106	311	3·8
30+	1713	68	4·0	240	12	5·0	85	7	8·2	2038	87	4·3
Total	8474	314	3·7	2187	117	5·3	792	69	8·7	11453	500	4·4
Child's civil status												
Legitimate	7810	265	3·4	1812	88	4·9	551	34	6·2	10173	387	3·8
Illegitimate	651	49	7·5	373	29	7·8	240	35	14·6	1264	113	8·9
Total	8461	314	3·7	2185	117	5·4	791	69	8·7	11437	500	4·4
Education of primiparae												
Minimum	1783	78	4·4	668	51	7·6	239	25	10·5	2690	154	5·7
More	1591	62	3·9	342	13	3·8	92	1	1·1	2025	76	3·8
Total	3374	140	4·1	1010	64	6·3	331	26	7·9	4715	230	4·9
Smoking (cigarettes/day)												
0	4940	137	2·8	1028	39	3·8	347	28	8·1	6315	204	3·2
1–10	1252	52	4·2	364	25	6·9	146	21	14·4	1762	98	5·6
11+	1945	114	5·9	706	49	6·9	274	20	7·3	2925	183	6·3
Total	8137	303	3·7	2098	113	5·4	767	69	8·9	11002	485	4·4
Parity												
0	3784	161	4·3	1096	69	6·3	396	36	9·1	5276	266	5·0
1–2	4382	137	3·1	1009	41	4·1	343	27	7·9	5734	205	3·6
3+	308	16	5·2	83	7	8·4	53	6	11·3	444	29	6·5
Total	8474	314	3·7	2188	117	5·3	792	69	8·7	11454	500	4·4

statistically significant in every case, but that when all characteristics were considered together, the only variables for which the associations were statistically significant were uncertainty of gestation and parity (Table 8).

'Spontaneous' preterm delivery. Only 63% of 'spontaneous' preterm deliveries were in women of certain gestation (Table 4). Preterm delivery occurred more often when the gestation was uncertain (9%) than when it was certain (4%) and again the gradient was steeper than with any of the maternal characteristics except illegitimacy. This gradient with unertainty persisted with separate categories of maternal characteristics with the exception of social class I–IIINM, and 'more than minimum' education. The analysis of variance (Table 7) showed that both the gradients with uncertainty and with maternal characteristics were highly statistically significant in every case, but that when all characteristics were considered together (Table 8) the only variables which were statistically significantly associated were uncertainty, parity and the child's civil status.

Mean birthweight. In pregnancies delivered at ≥37 weeks (Table 5) mean birthweight was 3354 g in those with certain gestation and 3262 g in the uncertain group. This was a steeper gradient than that with any of the maternal characteristics studied, and the decline in birthweight with uncertainty of gestation persisted within each category of maternal characteristics. The

Table 5. Mean birthweight (g) by certainty of gestation and maternal characteristics in deliveries at ≥37 weeks

	Certainty of gestation							
	Certain		Approximate		Uncertain		Total	
Characteristic	Total	Mean birthweight (g)	Total	Mean birthweight (g)	Total	Mean birthweight (g)	Total	Mean birthweight (g)
Social class of married women								
I–IIINM	2732	3404	481	3364	144	3338	3357	3395
IIIM	2648	3355	684	3284	186	3279	3518	3337
IV–V	1963	3317	545	3302	169	3221	2677	3308
Total	7343	3363	1710	3312	499	3276	9552	3349
Age (years)								
14–19	633	3268	352	3233	197	3230	1182	3251
20–29	5769	3351	1460	3304	425	3254	7654	3337
30+	1615	3395	217	3299	75	3363	1907	3387
Total	8017	3354	2029	3291	697	3262	10743	3336
Child's civil status								
Legitimate	7416	3362	1687	3311	497	3280	9600	3349
Illegitimate	588	3242	340	3194	199	3218	1127	3223
Total	8004	3353	2027	3291	696	3262	10727	3335
Education of primiparae								
Minimum	1668	3270	608	3227	208	3229	2484	3256
More	1507	3319	324	3278	84	3200	1915	3307
Total	3175	3293	932	3244	292	3221	4399	3278
Smoking (cigarettes/day)								
0	4729	3421	969	3389	303	3390	5551	3414
1–10	1172	3295	334	3198	124	3215	1630	3269
11+	1793	3207	643	3168	246	3111	2682	3189
Total	7694	3352	1946	3283	673	3256	10313	3333
Parity								
0	3541	3291	1007	3236	346	3208	4894	3274
1–2	4192	3403	948	3339	308	3312	5448	3387
3+	284	3411	75	3435	43	3340	402	3408
Total	8017	3354	2030	3291	697	3262	10744	3336

analysis of variance again showed that the gradients both with uncertainty and with maternal characteristics were highly statistically significant in every case (Table 7) but that when all maternal characteristics were considered together, the variables which remained significantly associated were uncertainty, parity, smoking and social class. In the pregnancies delivered at <37 weeks (Table 6), by contrast, the mean birthweight of the uncertain gestation group was greater at 2461 g than that of the certain group at 2250 g, and this persisted in each category of maternal characteristics. The normal gradient of greater birthweight with more favourable maternal characteristics was present. With small numbers, however, none of these effects was statistically significant in the analysis of variance (Table 7) except that of education in primiparae. However, when all characteristics were considered together (Table 8) the gradient with uncertainty was statistically significant.

Discussion

The analysis clearly shows that women with uncertain gestation have fewer favourable characteristics than those with certain gestation. For example, almost half of the women under 20 years of age and of single women have approximate or uncertain gestation. We would agree with Illsley & Thompson (1976) and Buekens *et*

Table 6. Mean birthweight (g) by certainty of gestation and maternal characteristics in deliveries at <37 weeks by certainty of gestation

	Certainty of gestation							
	Certain		Approximate		Uncertain		Total	
Characteristic	Total	Mean birthweight (g)	Total	Mean birthweight (g)	Total	Mean birthweight (g)	Total	Mean birthweight (g)
Social class of married women								
I–IIINM	129	2267	24	2271	7	2297	160	2241
IIIM	131	2321	44	2306	26	2517	201	2343
IV–V	115	2231	49	2129	17	2604	181	2238
Total	375	2248	117	2225	50	2516	542	2268
Age (years)								
14–19	46	2204	42	2278	33	2382	121	2278
20–29	298	2254	88	2203	41	2570	427	2274
30+	95	2257	21	2726	10	2273	126	2336
Total	439	2250	151	2297	84	2461	674	2284
Child's civil status								
Legitimate	376	2278	120	2221	46	2461	542	2281
Illegitimate	63	2082	31	2317	38	2461	132	2246
Total	439	2250	151	2241	84	2461	674	2274
Education of primiparae								
Minimum	115	2122	60	2171	31	2607	206	2209
More	84	2272	18	2086	8	2494	110	2257
Total	199	2186	78	2152	39	2584	316	2226
Smoking (cigarettes/day)								
0	203	2339	56	2423	37	2535	296	2379
1–10	77	2124	28	2137	20	2450	125	2179
11+	147	2196	61	2062	26	2397	234	2183
Total	427	2251	145	2216	83	2471	655	2271
Parity								
0	235	2194	87	2186	45	2443	367	2222
1–2	182	2303	56	2269	31	2467	269	2315
3+	22	2401	8	2633	8	2538	38	2479
Total	439	2250	151	2241	84	2461	674	2274

Table 7. Direction and significance of effect of certainty of gestation and various social characteristics separately upon pregnancy outcome

As increases	Perinatal mortality		Low birthweight		Spontaneous preterm delivery		Mean birthweight at >37 weeks		Mean birthweight at ≤37 weeks	
	Direction*	Significance†	Direction*	Significance†	Direction*	Significance†	Direction*	Significance†	Direction*	Significance†
Social class of married women										
Certainty	+	0·000	+	0·000	+	0·000	+	0·000	−	0·080
Social class	0	0·614	+	0·000	+	0·045	+	0·000	+	0·630
Interaction		0·263		0·580		0·046		0·293		0·164
Age										
Certainty	+	0·003	+	0·000	+	0·000	+	0·000	−	0·091
Age	−	0·181	∩	0·000	+	0·000	+	0 000	−	0·783
Interaction		0·000		0·002		0·014		0·236		0·863
Civil status										
Certainty	+	0·002	+	0·000	+	0·000	+	0 000	−	0·068
Civil status	0	0·900	+	0·000	+	0·000	+	0 000	+	0·276
Interaction		0·006		0·020		0·016		0·762		0·234
Education of primiparae										
Certainty	+	0·139	+	0·048	+	0·001	+	0 004	−	0 097
Education	0	0·807	+	0·000	+	0·000	+	0·000	+	0·040
Interaction		0·057		0·771		0·003		0·303		0·570
Smoking (cigarettes/day)										
Certainty	+	0·001	+	0·000	+	0·000	+	0·000	−	0 148
Smoking	0	0·503	+	0·000	+	0·000	+	0·000	−	0·095
Interaction		0·005		0·031		0·000		0·352		0 115
Parity										
Certainty	+	0·003	+	0·000	+	0 000	+	0·000	−	0·139
Parity	∩	0·008	∩	0·000		0·001	+	0·000	+	0·057
Interaction		0·001		0·295		0·548		0·113		0·965

* A positive/negative sign indicates that as certainty increases or maternal characteristics become more favourable, then the outcome is better/worse No sign has been given for the interaction term as the main interest is in whether or not it is significant. ∩ indicates that the central categories have a more favourable outcome than the extreme categories.

† The values in the significance column are the P values of an F ratio test

Table 8. Direction and significance of effect of certainty of gestation and various maternal characteristics upon pregnancy outcome (main effects only)

Characteristic	Perinatal mortality		Low birthweight		Spontaneous preterm delivery		Mean birthweight at >37 weeks		Mean birthweight at ≤37 weeks	
	Direction	Significance	Direction	Significance	Direction	Significance	Direction	Significance	Direction	Significance
Social class of married women	−	0·768	+	0·119	+	0·203	+	0·000	∩	0·706
Maternal age	−	0·545	+	0·284	0	0·119	−	0·123	0	0·239
Child's civil status	+	0·275	−	0·261	−	0·018	+	0·889	0	0·759
Smoking (cigarettes/day)	−	0·821	+	0·204	+	0·241	−	0·000	∩	0·805
Parity	+	0·079	∩	0·001	∩	9·009	+	0·000	+	0·061
Certainty	+	0·038	+	0·010	+	0·025	+	0·000	−	0·009

For conventions used in Table, see footnotes to Table 7 *al.* (1984) that exclusion of this group from epidemiological studies will introduce bias.

When considering a wide range of pregnancy outcomes, the only one with which uncertainty of gestation seemed to be favourably associated was mean birthweight before 37 weeks gestation. Possible explanations would include a tendency to underestimate the uncertain gestation lengths, or a tendency to overestimate the degree of uncertainty when larger babies are born before 37 weeks. In any event, numbers are small for this pregnancy outcome. For most outcomes, uncertainty is clearly and significantly associated with adverse outcomes, so that as many as 37% of women with a perinatal death, 34% of women with a low-birthweight baby, and 37% of 'spontaneous' preterm deliveries are excluded if only those of certain gestation are considered.

Important new conclusions from this analysis are first that the high rate of adverse outcomes associated with uncertainty of gestation is unlikely to be simply attributable to the unfavourable sociodemographic characteristics of women with uncertain or approximate gestation, since it occurs even when the analysis is controlled for a variety of such characteristics, as in our study. Furthermore, uncertainty of gestation, as we have defined it, actually 'explains' most of the adverse outcomes *better* than any of the traditional sociodemographic variables used in our analysis. This suggests that uncertainty of gestation may be identifying some behavioural and/or physical trait not identified by the factors usually considered, but which has an important association with adverse outcomes. This is analogous to the poorer prognosis recorded by the Coronary Drug Project Research Group (1980) in non-compliers (irrespective of whether the treatment to which compliance was expected was a pharmacologically active preparation or a placebo) and highlights the limitations of research using observational data. Since adequate data on uncertainty of gestation are not usually available, serious bias will certainly occur if women with uncertain gestation are excluded from studies, and the extent of the bias will be impossible to estimate if exclusions are made on an *ad hoc* basis.

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Chronic polyhydramnios is a syndrome with a lactogen receptor defect in the chorion laeve

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Summary. Human chorion laeve contains a lactogenic hormone [prolactin (PRL), growth hormone (GH) and placental lactogen (hPL)] receptor. Here, we studied binding of the potent lactogen, human GH, to this receptor in 18 normal pregnant women, in 12 patients whose pregnancies were complicated by chronic polyhydramnios and in 13 with chronic oligohydramnios. Polyhydramnios was classified clinically as idiopathic in seven patients, and secondary and associated with various disorders in the remaining five patients. Lactogenic hormone binding was lower in association with polyhydramnios (mean 1·60, SEM 0·15%) than with normal amniotic fluid volume (mean 3·05, SEM 0·40%; $P<0{\cdot}05$); Scatchard analysis indicated that a reduced number of lactogen receptors within the chorion laeve was the reason. The lactogenic hormone receptor defect in the chorion laeve was present in pregnancies complicated by either idiopathic or secondary polyhydramnios. In contrast to chronic polyhydramnios, tissue from patients with chronic oligohydramnios bound lactogenic ligands in a normal fashion. Insulin binding sites were also identified in the chorion laeve, and, in contrast to the lactogens, binding parameters were equivalent in the three patient groups. PRL resistance developing subsequent to this chorion laeve receptor defect might produce the excessive amniotic fluid volume characteristic of polyhydramnios. We propose that a chorionic PRL receptor deficiency underlies the various clinical forms of chronic polyhydramnios.

Prolactin (PRL) is a major regulator of water and electrolyte balance in amphibians, lower vertebrates and mammals (Bern & Nicoll 1968; Horrobin 1980). In man, PRL does not appear to have a direct action upon renal function (Carey *et al.* 1977) but can influence water and ion membrane fluxes across human 'fetal membranes' (Josimovich *et al.* 1977, Leontic *et al.* 1979) These 'membranes' are the amnion and chorion laeve, tissues of fetal origin which enclose the fetus and the amniotic fluid and are apposed to maternal endometrial decidual tissue.

Recent nucleic acid hybridization experiments demonstrated PRL messenger ribonucleic acid (mRNA) in human decidua of term gestation (Clements *et al.* 1983). This confirms and extends earlier reports of PRL synthesis by this tissue (Golander *et al.* 1978; Healy

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et al. 1979). Moreover, binding sites of PRL and the other lactogenic hormones, human growth hormone (hGH) and placental lactogen (hPL) to a common lactogen hormone receptor have been demonstrated in chorion laeve (Herington *et al.* 1980; McWey *et al.* 1982) while PRL has been localized immunohistochemically to amniotic epithelial cells (Healy *et al.* 1977; McCoshen *et al.* 1982*b*) and shown to pass across the chorioamnion to reach amniotic fluid in high concentrations (Riddick & Maslar 1981; McCoshen *et al.* 1982*a*). These results suggest that the chorioamnion membranes, tissues of fetal origin, may be the major site of control of amniotic fluid volume.

Polyhydramnios is a pregnancy complication where the amniotic fluid volume at term typically exceeds 1500 ml (Queenan & Gadow 1970). Although a number of theories have been proposed for the development of polyhydramnios, its cause remains unexplained. By late human pregnancy, amniotic fluid exchanges at a rate approaching 500 ml/h (Benson & Joseph 1961). Although this exchange is mainly diffusional water movement, it remains possible that abnormalities in the mechanism controlling such water transfer could result in significant amniotic fluid accumulation. Although fetal voiding and swallowing of amniotic fluid may reach 650 and 300 ml/day respectively at term, these rates are similar in normal and polyhydramniotic pregnancies and another mechanism produces the excessive increase of amniotic fluid water and electrolytes characteristic of polyhydramnios (Waldimoroff & Campbell 1974; Abramovich *et al* 1979). Idiopathic polyhydramnios comprises the largest subset of patients with excessive amniotic fluid volume and we recently demonstrated a lactogenic hormone receptor defect in the chorion laeve of pregnancies complicated by chronic idiopathic polyhydramnios (Healy *et al.* 1983).

We have now studied patients from all clinical subsets of chronic polyhydramnios and have observed a chorionic receptor defect for lactogens in each case, regardless of their apparent idiopathic or secondary nature. We have also compared the lactogen binding characteristics from pregnancies of excessive and normal amniotic fluid volume with those from oligohydramniotic pregnancies, where the volume is reduced or absent. Finally, we have compared lactogenic hormone with insulin binding to their respective chorion laeve receptors as a further index of the functional integrity of these membranes in these various pregnancy complications.

Patients and methods

Patients with polyhydramnios

Twelve consecutive patients with chronic polyhydramnios were studied. All had

Table 1. Clinical details of patients with chronic polyhydramnios

Patient no.	Parity[a]	Duration of Polyhydramnios (weeks)	Other antenatal complications	Gestation at delivery (weeks)	Amniotic fluid volume at amniotomy (l)[b]	Birth-weight (g)
1	1+0	6	—	36	3·1	3880
2	0+0	4	—	40	?	2460
3	1+0	4	—	35	2·8	2580
4	0+0	4	Breech	38	4·1	1965
5	2+1	3	—	37	?	3650
6	2+0	4	—	39	2·0	4000
7	0+0	5	—	38	1·9	4000
8	2+0	3	Twins, APH	34	?	2260
9	1+0	8	Anencephaly	44	2·1	3300
10	1+0	6	Insulin-dependent diabetic	39	1·8	4210
11	2+0	4	Insulin-dependent diabetic	39	2·2	4300
12	0+0	3	Pre-eclampsia	38	4·5	2720

[a] 2+1: 2 previous births plus one abortion.

[b] Patients 2, 5 and 8 ruptured membranes spontaneously.

APH, Antepartum haemorrhage.

polyhydramnios for ≥3 weeks in the third trimester of pregnancy. Idiopathic chronic polyhydramnios was defined as when diagnosed in singleton pregnancies without apparent cause Patients nos 1–7 were of this type as detailed in Table 1. In multigravid patients there was no past history of polyhydramnios. All patients were admitted to the antenatal ward for rest and investigation. The diagnosis of polyhydramnios depended upon a fundal height of ≥5 cm above the mean for that gestation, a tense uterus, difficulty in palpating fetal parts and excessive abdominal striae. Ultrasonography confirmed a gross excess amniotic fluid volume in each patient. Nine subjects did not have a spontaneous rupture of the membranes: their median amniotic fluid volume was 2·7 litres (range 1·8–4·5). In another woman (patient 8), removal of 1 litre of fluid by amniocentesis was necessary at 31 and 32 weeks gestation to relieve maternal distress: gross polyhydramnios had reformed when premature rupture of the membranes followed an antepartum haemorrhage. Patients 1, 6, 8 and 11 were delivered by caesarean section. Patients 10 and 11 were insulin-dependent diabetics but 50 g oral glucose tolerance tests were normal in all other patients.

No rhesus isoimmunization was found although mild ABO incompatibility developed in the baby of patient 1. Two babies died: one (no. 4) was born with trisomy 18 and died 3 days after birth while an anencephalic infant (no. 9) lived 2 days. Additional babies underwent surgery for oesophageal atresia (no. 12) and unexplained ascites (no. 3), apparently due to a spontaneous perforation of the bile duct. No patient had a placental chorioangioma but a single amnion and chorion was identified in the twin pregnancy (no. 8).

Control population and patients with oligohydramnios

The 18 pregnancies in the control population had normal amniotic fluid volumes, as assessed clinically and ultrasonically. Seven patients were delivered by elective repeat caesarean section. All pregnancies were otherwise obstetrically normal.

Thirteen consecutive patients with chronic oligohydramnios or anhydramnios were also studied. Oligohydramnios was defined as markedly reduced amniotic fluid volume as assessed clinically and ultrasonically (amniotic fluid pocket' or 'window' <1 cm^2) as well as finding <30 ml of fluid released at amniotomy (Manning *et al.* 1981). The mean gestation at delivery for these patients was 41 weeks (range 36–43 weeks). One patient carried an anencephalic fetus and two women required caesarean section for fetal distress in labour. Mean birthweights of infants from pregnancies with excessive, normal and low amniotic fluid volumes were statistically similar.

Chorion laeve preparation

Chorion laeve was taken at least 5 cm from the torn edge of amniochorion through which the infant had been born and 5 cm from the placenta. Each chorion laeve sample was placed immediately into 0·3 M sucrose containing 7100 kallikrein-inhibiting units (Trasylol, Bayer AG, West Germany) and stored frozen. The tissues were weighed and homogenized in 0·3 M sucrose using a Polytron (setting 4; 10 s; Brinkmann Instruments, Westbury, NY), followed by sonication (Branson Sonifier B-30, Danbury, CT; setting 1, 15 s) and were then centrifuged at 45 000 *g* for 60 min, and each resulting pellet was resuspended in a minimal volume of 25 mM Tris-HCl buffer (pH 7.5). Each pellet was then depleted of endogenous PRL by adding 2 ml 4 M $MgCl_2$ for 20 min at 4°C (Gerasimo *et al.* 1979) The suspension was diluted to 20 ml with 25 mM Tris-HCl buffer (pH 7·5) containing 10 mM $CaCl_2$ and was centrifuged at 45 000 *g* for 45 min. A second wash with Tris buffer followed. All protein concentrations were measured by the method of Lowry *et al.* (1951).

Binding studies

Binding studies using [^{125}I]-hGH (80–90 μCi/μg) were carried out essentially as described previously (Herington *et al.* 1976). Incubations were carried out in 25 mM Tris-HCl buffer (pH 7·4) containing 10 mM $CaCl_2$, 0·1% (w/v) BSA, and 0·02% (w/v) sodium azide at room temperature (20–22°C) for 18 h, at which time binding equilibrium was established. Specific binding was calculated as the difference in binding for [^{125}I]-hGH (0·2 ng: 20 000 ct/min) incubated in the presence and absence of a 5000-fold excess of unlabelled hGH.

hGH, a potent lactogen in primate and non-primate systems (Kleinberg & Todd 1980; Tanaka *et al.* 1980), has been widely used as a lactogenic receptor ligand in preference to or as a substitute for human PRL (hPRL), principally because it is more stable, aggregates less on storage, and is more easily iodinated than hPRL. [^{125}I]-hGH has been shown by us (unpublished data) and others to have qualitative binding characteristics similar to those of [^{125}I]-hPRL in lactogen receptor systems such as rabbit mammary gland membranes (Shiu & Friesen 1974*a,b*) or T47D human breast cancer cells (Shiu 1979), and in normal human chorion laeve (Healy *et al.* 1983) (mean [^{125}I]-hGH specific binding, 3·31% ($n = 9$); [^{125}I]-hPRL, 3·7% ($n = 3$)). In the present study, all direct comparisons between normal and poly- or oligo-hydramniotic pregnancy tissues were made using [^{125}I]-hGH as the sole lactogenic ligand.

Insulin binding to chorion laeve used porcine insulin (monocomponent, Novo Industries, Copenhagen, Denmark) iodinated by the chloramine-T method to a specific activity of approximately 150 μCi/μg. Incubations were carried out in 25 mM Tris-HCl buffer (pH 7·4) containing 0·1% (w/v) BSA and 0·02% (w/v) sodium azide at 4°C for 18 h. Specific binding was calculated as the difference in binding for [^{125}I]-insulin incubation in the absence (total binding) or presence of 4 U actrapid insulin (Novo; non-specific binding).

The hPRL and hGH used for iodination were gifts from the National Hormone and Pituitary Program of the NIADDKD (Bethesda, MD). The hGH used for standards was provided by the Commonwealth Serum Laboratories (Melbourne, Australia) Results are expressed as mean (SE) All binding studies were carried out at a membrane concentration of 200 μg protein/tube. The Wilcoxon non-parametric test for unpaired data was used to compare results in the study groups.

Results

Comparison of lactogen binding in patients with polyhydramnios, oligohydramnios and normal amniotic fluid volume

The percentage specific binding of [^{125}I]-hGH to chorion laeve from pregnancies with excessive, normal or low amniotic fluid volume is displayed in Fig. 1. Specific binding of [^{125}I]-hGH was significantly lower ($P<0·05$) in pregnancies complicated by chronic polyhydramnios than in pregnancies with normal or low fluid volume.

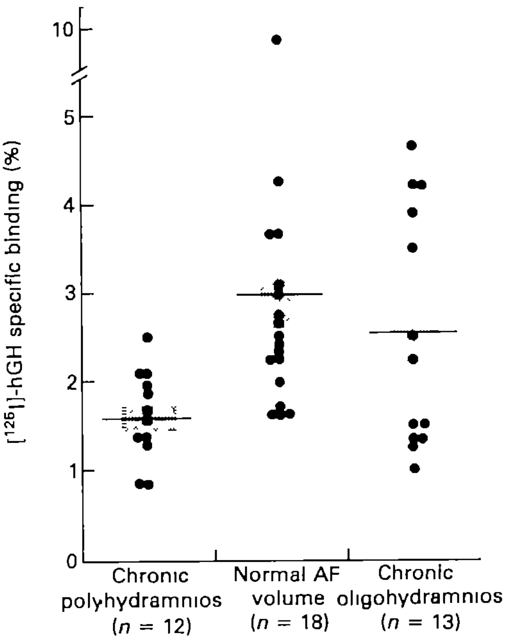

Fig. 1. [^{125}I]-hGH specific binding to chorion laeve membranes from pregnancies with normal amniotic fluid (AF) volume, chronic polyhydramnios and chronic oligohydramnios. Ligand binding was significantly reduced in tissue from chronic polyhydramniotic pregnancies ($P<0·05$). The stippled zone indicates 1 SE about the mean

There was no direct or inverse correlation between fluid volume and chorionic lactogen binding. Non-specific binding of GH was low and equivalent in both normal and hydramniotic tissues [1·71 (SEM 0·11)% and 2·00 (SEM 0·14)% of the total counts added, respectively]. Hormone binding characteristics were similar regardless of vaginal or caesarean birth ($n=6$). Fig. 2 compares lactogen binding between pregancies complicated by chronic idiopathic or secondary polyhydramnios. Binding was similar between these two patient groups.

Scatchard analysis of the binding characteristics of lactogens to chorion laeve revealed a single class of binding site in tissue from both normal and hydramniotic pregnancies. In five preparations from pregnancies with normal amniotic fluid volume, binding affinity was 0·47 (SEM 0·10)×10^9 l/mol while binding capacity equalled 175·2 (SEM 56·0) fmol/mg protein: equivalent results were obtained in three oligohydramniotic chorion samples. By contrast, chorion from polyhydramniotic gestations of idiopathic or secondary type displayed a

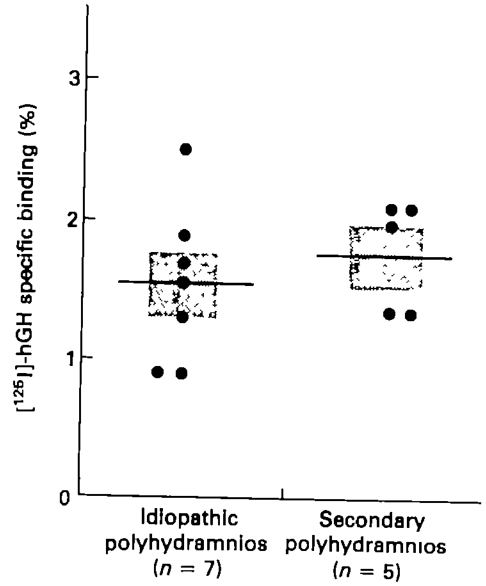

Fig. 2. Comparison of $[^{125}I]$-hGH binding between pregnancies complicated by either chronic idiopathic or secondary polyhydramnios. The stippled zone indicates 1 SE about the mean.

reduced concentration of lactogen binding sites [53·5 (SEM 19·0) fmol/mg protein; $n = 3$; $P < 0{\cdot}05$] but comparable binding affinities to those observed in normal and oligohydramniotic chorion laeve.

Comparison of insulin binding in patients with polyhydramnios, oligohydramnios and normal amniotic fluid

To determine if the loss of lactogenic hormone receptors in the chorion laeve was non-specific and due to damage to the cell membrane as a consequence of polyhydramnios, insulin binding to normal and hydramniotic membranes was measured. High-affinity, low-capacity insulin binding sites were identified in each of the three tissue groups. Insulin binding was similar for membranes from normal, polyhydramniotic and oligohydramniotic pregnancies (Table 2). Non-specific binding of insulin for all membrane preparations was low [0·53 (SEM 0·2)% and 0·78 (SEM 0·40)%, of the counts added, respectively, for normal and hydramniotic tissues].

Discussion

Polyhydramnios is a major obstetric complication associated with increased perinatal morbidity. Typically, no cause is found for chronic polyhydramnios although clinical associations include diabetes mellitus, fetal malformations—especially oesophageal atresia and anencephaly, rhesus isoimmunization, twin pregnancy and placental chorioangioma. Even in these cases, however, the precise mechanism whereby excess fluid accumulates is unclear. There is no direct correlation between amniotic fluid glucose concentration and fluid volume (Dewhurst 1976). Oesophageal ligation in the fetal monkey does not produce polyhydramnios (Wintour 1981), suggesting that it is not the oesophageal atresia *per se* which increases fluid volume, while normal amniotic fluid volume and even oligohydramnios can occur in the presence of an anencephalic fetus, indicating the fetal defect alone is not responsible for the excessive fluid accumulation.

Table 2. Binding of ^{125}I-insulin to chorion laeve

Membrane preparation	% specific binding	
	Mean (SE)	(n)
Normal pregnancies	19·3 (3·1)	10
Chronic polyhydramnios	15·3 (1·8)	6
Chronic oligohydramnios	19·7 (2·5)	7

Previously, we have found a lactogenic hormone receptor defect in the chorion laeve of patients with chronic idiopathic polyhydramnios (Healy *et al.* 1983). This defect seems due to a reduced concentration of lactogen receptors. We have now investigated a number of other recognizable disorders. The same lactogen receptor defect has been observed. This novel finding indicates a role for lactogenic hormones in the pathogenesis of polyhydramnios. Of interest, however, is the observation that only PRL seems important for this function. Despite the binding of hGH to chorion laeve, neither hGH nor chorionic somatomammotrophin (placental lactogen) influenced osmoregulation when applied in equimolar concentrations to amnion *in vitro* (Leontic & Tyson 1977). Confirmation of this action of PRL upon tritiated water transport across human amnion/chorion/decidua has recently appeared (Tyson *et al.* 1983). In contrast to polyhydramnios, chorion laeve lactogen binding is preserved in oligo- or an-hydramnios. Lactogen and insulin receptor concentrations and ligand affinities were similar in oligohydramnios and pregnancies with normal fluid volumes (Fig. 1, Table 2). Such normal binding implies that the lactogen receptor in chorion laeve is not the defective locus responsible for the inexorable decrease in amniotic fluid seen in chronic oligohydramnios. It remains possible that some post-receptor abnormality within the lactogen binding site in the amniochorion produces oligohydramnios.

We have also demonstrated in this study that insulin binding to chorion laeve is normal in polyhydramnios. Preservation of the integrity of the insulin receptor in the chorion laeve indicates that the reduced lactogenic hormone binding which we observed in this tissue was not due to tissue degeneration. Although this is the first report formally to describe insulin binding sites in the chorion laeve, insulin receptors have been previously identified in the embryologically identical chorion frondosum upon the syncytiotrophoblast microvillus membrane (Posner 1974; Whitsett & Lessard 1978; Harrison & Itin 1980). Our data support the concept that resistance to PRL action at the amniochorion, resulting from loss of receptors, produces impaired water transport and subsequent polyhydramnios (Leontic & Tyson 1977; Leontic *et al.* 1979; Herington *et al.* 1980; Healy *et al.* 1983). A similar deficiency in the number of hormone receptors has also been found for insulin in obese diabetics, low-density lipoprotein in familial hypercholesterolemia, progesterone in pseudocorpus luteum insufficiency and testosterone in androgen insensitivity (Harrison & Roth 1980; Griffin 1979; Keller *et al.* 1979).

The lactogen receptor defect was present not only in idiopathic polyhydramnios but also in patients with diabetes mellitus, twin pregnancy, oesophageal atresia and anencephaly (Table 1). These results imply that the same defective chorionic PRL binding site locus is involved in the pathogenesis of chronic polyhydramnios of any form. Indeed, PRL receptor loss in the single chorion laeve of a uniovular twin pregnancy would be consistent with the frequent development of polyhydramnios seen in this type of multiple gestation (Table 1; patient 8). One might also anticipate a chorionic receptor abnormality to develop in the neoplastic chorion of a placental chorioangioma. We do not yet know the water flux across the amniochorion from polyhydramniotic pregnancies nor what endogenous ligands regulate the chorion laeve PRL receptor. Our demonstration of a lactogenic hormone receptor defect in the chorion laeve suggests PRL resistance at this binding site as a new and unifying explanation for the development of chronic polyhydramnios.

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James Barlow (1767–1839): operator of the first successful caesarean section in England

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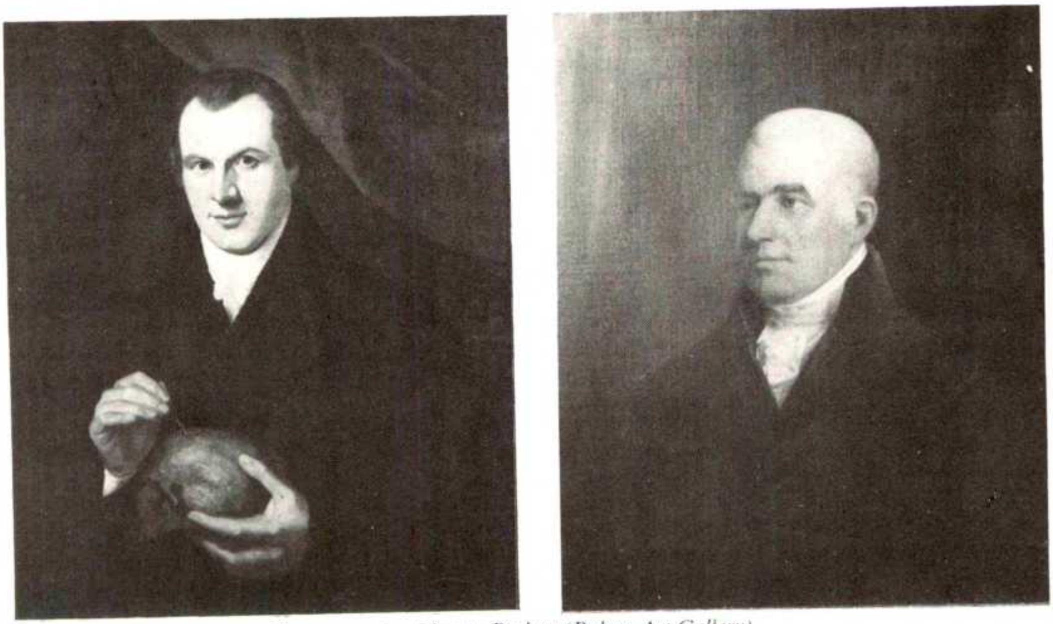
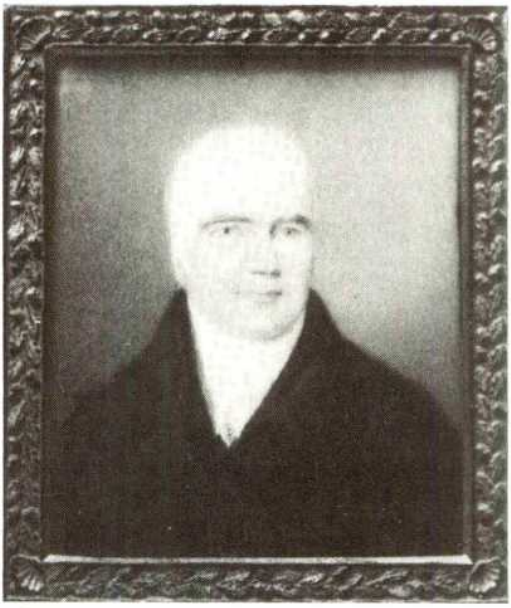


Two portraits of James Barlow (Bolton Art Gallery).

In 1500, the first recorded caesarean section on a living women was done by a Swiss sow gelder, Jacob Nufer, on his own wife, but no published record appeared until 1582 (Young 1944). In Great Britain the first caesarean section on a living woman was performed in Edinburgh by Robert Smith on 29 June 1737, but the mother died some hours after the operation. In 1738 an Irish midwife, Mary Donally, was said to have carried out such an operation using a razor, and in order to stitch the wound she waited whilst someone walked a mile to fetch the silk (Cone 1974); since no medically qualified person was involved and no first-hand record kept this mysterious case is generally discounted. During the remaining part of the eighteenth century there were about a dozen records of a reputable medical practitioner performing a caesarean section but in no instance did the mother survive, though a few children were saved.

In 1793 James Barlow, a Lancashire surgeon, whilst practising in Chorley performed a caesarean section on a woman in the village of Blackrod, near Bolton. It is the first operation of its kind in Great Britain where the life of the mother was saved.

James Barlow was born in 1767 at Croichley Fold Farm, Hawkshaw, which is now in the postal district of Bury. It is not known at which medical school he was taught but the dedications in his textbook indicate a close acquaintance with Abernethy whose anatomy lectures he may have attended at St Bartholomew's Hospital. In 1790 he established himself in practice at Chorley and soon acquired a reputation as a skilled surgeon. In 1795 he



Miniature of James Barlow (Blackburn Art Gallery).

married Elizabeth Winstanley, daughter of a rich Preston family but this marriage may well not have lasted more than a few weeks. The breakdown of the marriage perhaps persuaded James Barlow to leave Chorley and set up practice in Blackburn. He lived in a stone house off Dukes Brow called Bank House which was built in the mid-seventeenth century and still stands today in extremely good condition; it is one of the oldest houses in Blackburn. In 1826 he built a brick house nearby bearing his initials and family crest, which is now part of a Girls' School (McQuay 1965). He never married again but in 1812 adopted a son, James Barlow Stewardson Sturdy, who later became Mayor of Blackburn. In his will dated 28 December 1833, Barlow bequeathed the bulk of his estate to Sturdy 'whom I have brought up from his infancy'. This included his house, Spring Mount, two other dwellings, a proportion of his household furniture, his library, pictures, surgical instruments, shares in the Blackburn Gas Company and in the New Turnpike Road from Blackburn to Preston, and any ready money. The estate, which included a few minor bequests, was valued for probate at under £9000.

James Barlow published a detailed account of his successful caesarean section in *Medical Records and Researches* (Barlow 1798) and later in his book *Essays on Surgery and Midwifery* a 400-page monograph (Barlow 1822). He wrote:

> *Jane Foster the subject of the following case, resides in the village of Blackrod about 5 miles from Chorley and is about 40 years of age, of robust constitution and has had several children.*

Dr Barlow was invited to see this patient by a surgeon from Wigan, Mr Hawarden, because the midwife had reported no progress after several days of labour. He performed a vaginal examination after eliciting a past history of an injury to her pelvis in a cart accident and recorded his opinion:

> *On conversing with Mr. Hawarden concerning the nature of the case and the impossibility of bringing the child away through the natural passage, the only alternative was Caesarean section but the well-known danger of this induced Mr. Hawarden to decline*

> *taking part in it and he returned home. Convinced therefore of the impossibility of affecting delivery by any other means it was proposed to the* [patient's] *attendants but was not consented to.*

Next day 27 November 1793, Wednesday, he was called again when the patient agreed to have the caesarean section. James Barlow wrote:

> *I immediately called in as an assistant Mr. Hawarden, a practitioner of the village of Blackrod and brother of Mr. Hawarden aforementioned. The patient being taken out of bed and placed upon a table laying on her back with her head raised by pillows. I began by making a longitudinal incision 5½" in length as high as the navel, parallel to linea alba and about 2" to the left of that line. The integuments and the left rectus muscle being cut through, a small opening was made through the peritoneum. The uterus was now exposed to view and an incision of the same length was continued through it. The child presented itself with its breech and was extracted through the artificial opening but unfortunately was dead.*

A footnote at this stage makes the event much more dramatic.

> *At the commencement of the operation Mr. Hawarden was suddenly seized with a violent fit of syncope which wholly incapacitated him from attending to the steps of the operation and having no other professional person present I was obliged to be assisted by a female attendant.*

Barlow concluded the operation by closing the abdomen and dressing the wound. This operation was performed almost 50 years before ether or chloroform were introduced as anaesthetic agents, but:

> *the poor woman scarcely complained during the operation, so great was her fortitude. Soon after she was put to bed she slept without any medicine and passed a good night.*

He closely watched his patient for some days, removed the sutures on the sixth day, and allowed her out of bed in 2 weeks; she was engaged in domestic duties in three weeks. After seeing her on 23 September 1796 he recorded:

> *After an interval of nearly three years she has continued in health, menstruated with regularity and has never been pregnant.*

His last entry about this patient is found in one of his later publications of 1833, where it is mentioned that Jane Foster died in October 1829 and was interned in 'Bolton-le-Moors'. James Barlow's operative triumph was not repeated until 40 years later in 1834 by T. L. Greaves (Greaves 1834).

Soon after James Barlow's account of the operation, Dr William Simmons of Manchester published his strong opposition to caesarean section (Simmons 1798), completely ignoring Barlow's success. Within a fortnight John Hull wrote an equally strong reply in favour of caesarean section (Hull 1798). John Hull also criticised Barlow's operation and implied that he had not performed a caesarean section but merely removed the fetus from the peritoneal cavity. Such a suggestion is quite unfounded if Barlow's anatomically correct and scientific accounts are studied carefully, and it seems that professional jealousy and family feud might be at the root of Hull's criticism. John Hull married Sarah Winstanley who was the sister of Barlow's estranged wife.

Apart from the comprehensive record published by Barlow, the existence of Jane Foster can be confirmed from records available at the Lancashire Records Office in Preston. Jane Foster was born on Christmas Day 1753. Her father was William Watmough who married Mary France on 2 February 1741 at Deane Parish Church, Bolton; they had three sons and three daughters. Jane was their fourth child and was married to Henry Foster on 20 July 1773. She had seven children before her final pregnancy. According to these records her last living child was born on 29 March 1791 and christened on 17 April at St Catherine's, Blackrod. Her last pregnancy was in 1793 as described by James Barlow, and she survived long after this historical operation. The burial register of Bolton Parish Church contains an entry related to a Jane Foster who was buried on 13 October 1829. Her death was also announced in the columns of the *Bolton Chronicle* of 17 October 1829. At both these places her age has been recorded erroneously as 86, but there is sufficient evidence available to indicate that she was approaching her 76th birthday.

James Barlow was among the great pioneers in surgery during the early nineteenth century and working in a small town in Lancashire did not in any way handicap him. His surgical practice, as reflected from his writings, was based on modern scientific methods; he wrote authoritative texts on surgery, lectured and trained doctors. He inherited the sum of £12 000 upon the death of his father on 12 February 1815 and had a lucrative practice, but he never let his comfort interfere with his duty as a doctor. There is evidence that if called upon he would visit his patients at inconvenient times in severe weather. The *Blackburn Mail* of 15 August 1827 published the report of an accident when a coach overturned; James Barlow rushed to treat the injured and amputated the leg of a young woman at the site. He was also well-known for surgical treatment of stones in the bladder, recorded many case histories of interest and invented instruments to be used in such operations. He strongly advocated the use of pelvimeters. In 1822 he wrote:

> *though in this country pelvimeters are rarely used for gauging the pelvis, yet on an occasion of such vast importance, every means should be employed to attain this point as accurately as possible, for on our decision rests both the fate of the mother and of the unborn foetus entrusted to our protection.* (Barlow 1822)

James Barlow also had the distinction of being the first in Great Britain to suture the uterus after caesarean section. After the first caesarean section he performed three more, although the honour of performing more than one caesarean section is incorrectly bestowed on John Hull by J. H. Young (Young 1944). Barlow performed the fourth caesarean operation on 22 August 1825. The *Blackburn Mail* dated 30 August 1826 recorded this in their columns (Miller 1959):

> *On Tuesday 22nd inst., the Caesarean operation was performed on the wife of Edmund Forrest, of Samlesbury, in this neighbourhood, by Mr. Barlow, surgeon, of Blackburn. We are credibly informed that the child is alive and healthy, and that the mother survived the operation till Saturday morning. It is worthy of remark that this is the fourth instance of the kind which has occurred to this celebrated surgeon by which the lives of three children and one woman have been preserved.*

In his own account of this operation James Barlow gave additional notes which are worth recording. After the death of the patient some of his jealous fellow surgeons exhumed the woman's body and carried out an illegal postmortem investigation. The result of this was conveyed to James Barlow by a medical student present at this occasion, who also confirmed that deformity of the pelvis was found to be so great that caesarean section was imperative.

In his old age Barlow devoted his time to writing and teaching. His literary work shows him to be extremely puritanical and a man of great conviction. An additional publication of his exists in Blackburn Library entitled *An Address to Medical and Surgical Pupils on the Studies and Duties of their Profession* Barlow (1839) together with some manuscript material on the subject of cholera.

James Barlow claimed to be a descendant of Sir Alexander Barlow, one of whose sons Ambrose Barlow was hanged and quartered for his faith in 1641 at Lancaster Castle and canonized by the Pope in 1970. James Barlow died at his home on 20 August 1839 and was buried in Blackburn Parish Churchyard.

Acknowledgments

I am grateful to Miss A. Schofield and Bolton Art Gallery for permission to reproduce the portrait of James Barlow and to Alan Jackson, Department of Medical Illustration, Bolton General Hospital for preparing the photograph.

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A comparison of the effects of four intravenous solutions for the treatment of ketonuria during labour

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Summary. Forty women in whom ketonuria was detected during the first stage of labour were allocated randomly to intravenous treatment with one litre of either normal saline, Hartmann's solution, 5% dextrose or 10% dextrose. The solutions were administered over 1 h and blood was taken immediately beforehand and thereafter at 30-min intervals for 90 min to assess their effect on intermediary metabolism, plasma osmolality and acid–base status. Although both the 5 and 10% dextrose infusions caused a rapid decline in whole blood D-3-hydroxybutyrate concentrations, they also produced pathological degrees of maternal hyperglycaemia and hyperinsulinaemia and a marked elevation in the mean blood lactate and pyruvate concentrations. Administration of 10% dextrose was also associated with a significant increase in serum osmolality. Hartmann's solution produced significantly higher mean whole blood lactate and pyruvate concentrations than did normal saline. There was a significant increase in the venous base deficit in the group infused with 10% dextrose, indicating that the buffering capacity of the blood had been exceeded. It is concluded that rapid infusions of dextrose or Hartmann's solution should not be administered during labour. Normal saline should be used for rehydration and if dextrose therapy is deemed necessary the dose administered should not exceed physiological requirements.

Maternal ketonuria during labour is often treated with rapid, high-dose glucose infusions, in the belief that raised circulating ketone concentrations cause impaired myometrial function and prolonged dysfunctional labour (Dumoulin & Foulkes 1984). It is now generally accepted that ketone bodies are not waste products of metabolism but are readily available energy sources for the muscle and brain of both the mother and her fetus (Adam *et al.* 1973, 1976; Rudolf & Sherwin 1983). Evidence that secondary arrest in labour is attributable to ketonaemia is largely anecdotal (Foulkes & Dumoulin 1983) and the rationale for correcting ketonaemia in labour by intravenous dextrose infusion is questionable. In addition, it is not sufficiently recognized that administration of glucose causes a significant increase in blood lactate concentration. Lactate can be converted to glucose and in physiological quantities is a source of energy. It is often infused rapidly during labour in the form of Hartmann's solution, to 'preload' patients before epidural analgesia. However, it has been shown that the high concentrations of

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lactate in maternal blood during labour are associated with high concentrations in the fetus and cause a lowering of fetal pH (Lawrence *et al.* 1982). Previous studies have demonstrated the deleterious effects of fructose infusion (Pearson & Shuttleworth 1971) and of dextrose, fructose and sorbital infusions (Ames *et al.* 1975) on maternal and fetal blood lactate concentrations, but the infusion regimens used in those studies are not used in clinical practice. Indeed, the dose of glucose (100 g in 1 h) administered by Lawrence *et al.* (1982) was larger than that used in most centres. The effect of hyperglycaemia on serum osmolality and the relative influence of hyperlactataemia on the base deficit of maternal blood has not previously been reported.

This study was a randomized prospective comparison of the effects of four commonly used infusions, normal saline, 5 and 10% dextrose and Hartmann's solutions, on intermediary metabolites, the acid–base status of whole blood and serum osmolality in women with ketonuria during labour.

Patients and methods

Women who had developed significant ketonuria (Ketostix 2+) on routine urine testing during spontaneous, induced or augmented labour at 37 to 42 weeks gestation were recruited for study. Patients thought likely to give birth within 2 h of the start of the infusion were not recruited.

Forty patients were randomly allocated to one of four infusion groups: (1) normal saline; (2) Hartmann's solution; (3) 5% dextrose and (4) 10% dextrose. Venous blood was taken, without tourniquet, for measurement of glucose, insulin, lactate, pyruvate, D-3-hydroxybutyrate, base excess, pH and serum osmolality.

Venous blood (14 ml) was drawn at each sampling: a sample for blood gas analysis, 10 ml into lithium heparin and 2 ml into fluoride oxalate.

One litre of the randomly selected solution was then infused over 1 h and further blood samples were taken at 30 and 60 min. A slow normal saline infusion was then continued to maintain the intravenous cannula patency and a final blood sample was taken at 90 min. Immediately after sampling 1 ml of heparinized blood was added to 2 ml ice-cold 6% perchloric acid and mixed well. The perchloric acid, lithium heparin and fluoride oxalate samples were stored on ice until the end of the sampling period, when the samples were centrifuged. Plasma was stored at −20°C and the perchloric acid supernatant at −70°C until analysis.

Normal labour ward management was continued during the study and an oxytocin infusion was in progress in 17 patients (see Table 1), who received an additional 5% dextrose infusion at an average of 40 ml (2 g)/h. In a further 12 patients labour was augmented using oxytocin in 5% dextrose after the study had been completed.

Only one patient had epidural analgesia inserted before the infusion and a fluid 'preload' had not been given.

Blood gases were determined as soon after each sampling as possible using a Radiometer ABL3. Serum osmolality was determined using a wide-range osmometer, model 3W (Advanced Instruments Incorporated). Plasma glucose was measured using an automated glucose oxidase peroxidase method (Trinder 1969) and plasma insulin by means of a charcoal separation technique (Albano *et al.* 1972). Blood lactate, D-3-hydroxybutyrate and pyruvate were measured using a modification of the fluorimetric method of Lloyd *et al.* (1978).

Table 1. Patient details

Group	Maternal weight at delivery (kg)	Parity		Gestation (weeks)	Cervical dilatation at start of infusion (cm)	Labour			
		0	≥1			Spontaneous	Induced	Augmented at time of infusion	Epidural at time of infusion
Normal saline	78·5 (1·8)	4	6	40·3 (0·3)	3·7 (0·4)	3	7	2	1
Hartmann's solution	74·9 (3·8)	7	3	39·4 (0·5)	4·2 (0·4)	3	7	6	0
5% dextrose	71·6 (2·1)	4	6	40·0 (0·4)	3·6 (0·4)	4	6	2	0
10% dextrose	83·8 (5·1)	6	4	40·2 (0·4)	3·9 (0·5)	3	7	7	0

Results are mean (SD) where appropriate. $n = 10$ in each group.

The mean and standard error of the mean were calculated for each of the metabolites and other variables investigated. The statistical significance of the differences between and within groups were evaluated with paired and unpaired *t*-tests as appropriate.

Results

The groups were comparable with regard to parity, gestation, number of induced and spontaneous labours, and cervical dilatation at the time of commencing the infusion (Table 1). Despite random allocation the mean maternal weight at delivery of the group receiving 10% dextrose was significantly higher than that of the saline-treated controls ($P<0{\cdot}005$).

The plasma glucose concentrations in the four groups are shown in Fig. 1. In the 10% and 5% dextrose groups, glucose concentration rose to a mean maximum at 60 min of 24·3 mmol/l and 16·2 mmol/l respectively and remained constant at approximately 5 mmol/l in the other two groups. Significant insulin responses occurred in both groups receiving dextrose (Fig. 2).

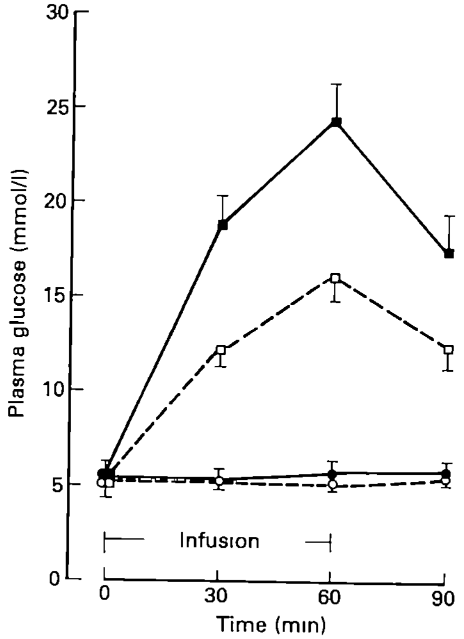

Fig. 1. Mean plasma glucose concentrations in the four study groups. ○ Normal saline; ● Hartmann's solution; □ 5% dextrose; ■ 10% dextrose. $n=10$ in each group. The vertical lines represent the SEM values.

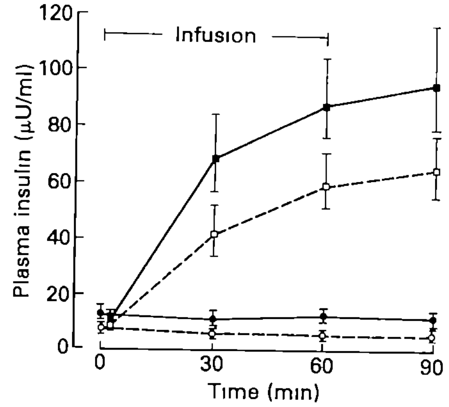

Fig. 2. Mean plasma insulin concentrations in the four study groups. Symbols as in Fig. 1.

The changes in blood D-3-hydroxybutyrate concentrations are shown in Fig. 3. Both 5% and 10% dextrose infusions produced a rapid and significant fall in maternal D-3-hydroxybutyrate ($P<0{\cdot}0001$). There was no significant change when normal saline or Hartmann's solution were infused.

A progressive increase in lactate concentration occurred in both groups of women receiving dextrose infusions (Fig. 4), and despite the fall in glucose concentrations blood lactate values continued to rise after the completion of the infusion. There was no significant difference

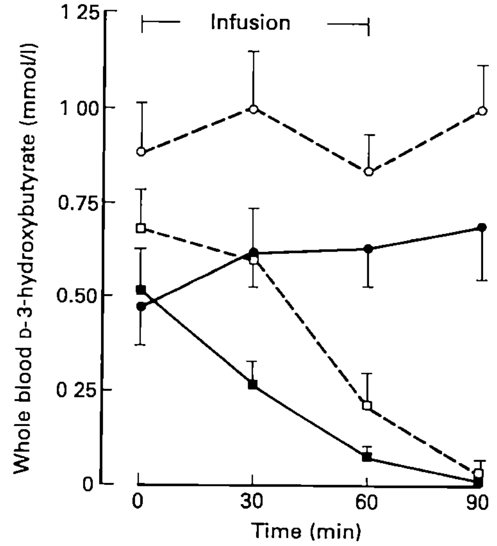

Fig. 3. Mean whole blood D-3-hydroxybutyrate concentrations in the four study groups. Symbols as in Fig 1.

at 90 min between the blood lactate concentrations of the women treated with 5 and 10% dextrose solutions. There was no significant change in lactate concentrations in the saline treated group. During the infusion of Hartmann's solution there was a significant increase in circulating lactic acid ($P = 0{\cdot}001$ at 60 min) and 30 min after stopping the infusion the blood lactate remained significantly elevated ($P = 0{\cdot}018$).

The change in blood pyruvate concentration in the four study groups mirrored the blood lactate concentrations (Fig. 5)

The serum osmolality of all subjects was within the normal range before the infusion but rose throughout the study in the group receiving 10% dextrose and was significantly greater than that in the other groups at 60 and 90 min ($P<0{\cdot}001$) (Fig. 6).

All patients receiving 10% dextrose developed glycosuria compared with only one patient in the 5% dextrose group and none in the other groups.

The changes in maternal venous blood pH and base deficit after the infusion are shown in Tables 2 and 3. There was a small increase in base deficit during the infusion in all groups. The greatest increase was observed in the group treated with 10% dextrose and the mean value at the end of the infusion in this group was significantly higher than that in the group receiving normal saline ($P = 0{\cdot}05$).

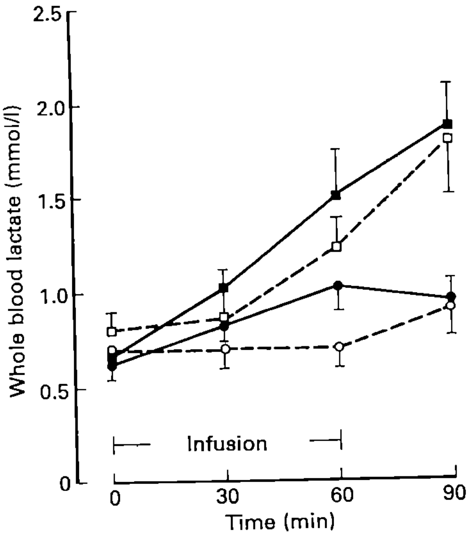

Fig. 4. Mean whole blood lactate concentrations in the four study groups. Symbols as in Fig. 1.

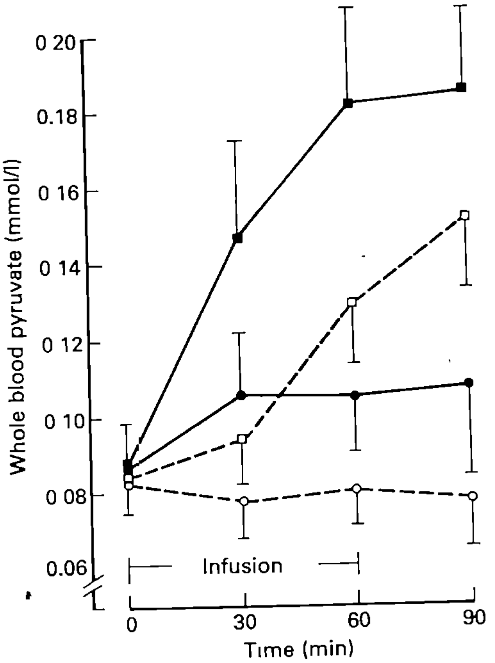

Fig. 5. Mean whole blood pyruvate concentrations in the four study groups. Symbols as in Fig. 1

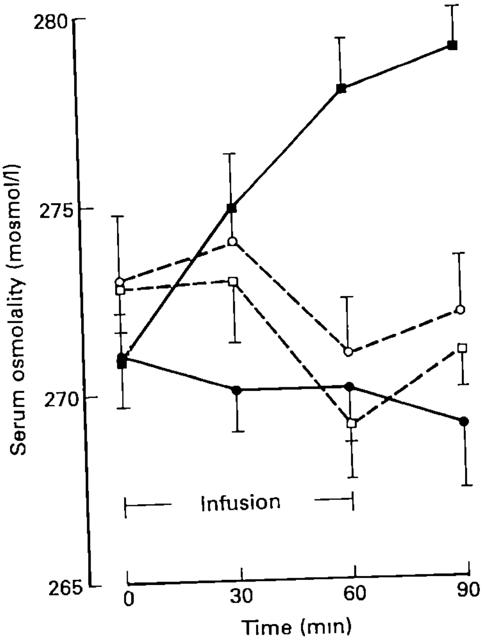

Fig. 6. Mean serum osmolality in the four study groups. Symbols as in Fig 1.

Table 2. Maternal venous blood pH before and after 60-min intravenous therapy for ketonuria in labour

Group	Time after start of infusion			
	Before	During		After
	0 min	30 min	60 min	90 min
Normal saline	7·424 (0·026)	7·401 (0·019)	7·395 (0·039)	7·403 (0·063)
Hartmann's solution	7·431 (0·020)	7·431 (0·037)	7·427 (0·042)	7·423 (0·05)
5% Dextrose	7·433 (0·035)	7·415 (0·046)	7·417 (0·04)	7·412 (0·019)
10% Dextrose	7·426 (0·032)	7·414 (0·033)	7·396 (0·029)	7·406 (0·04)

Results are mean (SD).

Table 3. Maternal venous blood base deficit (mEq/l) before and after 60-min intravenous therapy for ketonuria in labour

Group	Time after start of infusion			
	Before	During		After
	0 min	30 min	60 min	90 min
Normal saline	4·61 (1·17)	4·65 (1·05)	5·38 (1·35)	5·77 (1·37)
Hartmann's solution	4·02 (1·15)	4·49 (1·26)	4·90 (1·13)	4·75 (1·08)
5% Dextrose	4·15 (0·84)	4·64 (1·12)	4·33 (1·30)	4·79 (1·13)
10% Dextrose	4·80 (0·80)	5·49 (0·92)	6·52 (1·11)	6·68 (1·03)

Results are mean (SD).

There were no significant differences between any of the groups in the mean time from the onset of the infusion to delivery, the mode of delivery and the mean Apgar score.

Discussion

During labour, energy consumption is greatly increased and coupled with modern labour ward policy of starving the patient, ketonuria is a common finding. D-3-hydroxybutyric acid is the predominant ketone produced during labour (Bencini & Symonds 1972) and in this study concentrations comparable to those previously reported were observed (Borberg *et al.* 1980). This and other ketones can be used by both smooth and skeletal muscle as an energy source. Evidence that their presence impairs myometrial activity is based on anecdote and studies by Winkler & Hebeler (1939) who originally reported the association between ketosis and prolonged labour but gave no evidence to support the concept of a causal relation. In addition, urine dip-sticks, which detect acetoacetate, frequently give a positive result when the blood acetoacetate level is within the normal range (Coetzee *et al.* 1980).

The suggestion by Romney & Gabel (1966) that hypertonic glucose infusions are therapeutic in the treatment of fetal distress now seems untenable. Shelley *et al.* (1975) have shown that the plasma lactate concentration in fetal lambs rises and the pH falls with increasing glucose concentrations especially when there is fetal hypoxia. Similar findings were observed in a study of women undergoing caesarean section after dextrose loading (Kenepp *et al.* 1982). Myers (1978) demonstrated that a hypoxic insult to the fetal rhesus monkey is less damaging to the fetal brain when this follows a period of maternal starvation, compared with its effect after glucose infusion or after feeding.

It is unfortunate that despite randomization, the group infused with 10% dextrose was significantly heavier than the other groups. However, Metzger *et al.* (1982) have shown that lean and obese subjects are equally vulnerable to the development of ketosis during starvation.

In this study, both 10% and 5% dextrose infusion produced hyperglycaemia comparable to that seen in a poorly controlled diabetic. The resulting maternal hyperinsulinaemia inhibits hepatic lipolysis and ketone synthesis and replaces a physiological process of alternate substrate production with a pathological process leading to excessive lactate formation. Although no change in venous pH was observed, the buffering capacity of the blood was clearly exceeded in the 10% dextrose group as shown by the falling base excess. It seems illogical to suppress the concentration of the ketoacids at the expense of increasing other organic acids which place a greater strain on the buffering capacity of the blood.

The plasma glucose concentrations in the groups infused with saline and Hartmann's solution were slightly raised compared with the normal basal plasma glucose concentration in the pregnant state (Gillmer *et al.* 1975). Coltart *et al.* (1969) showed that fetal plasma glucose concentrations rise in parallel with those of the mother and the incidence of neonatal hypoglycaemia in infants of poorly controlled diabetic and hyperglycaemic non-diabetic patients is well known (Lucas *et al.* 1980). Lawrence *et al.* (1982) also demonstrated that fetal blood lactate concentrations rose during glucose infusion more slowly than in maternal blood, and that the rise continued after the infusion had ceased, but they investigated only the effects of 10% dextrose and saline infusions. In the present study the lactate concentrations were as high in the 5% dextrose as in the 10% dextrose group. Hartmann's solution also produced a significant rise in blood lactate concentrations, but had no effect on D-3-hydroxybutyrate concentrations. Administration of these solutions during labour would therefore be expected to cause an increase in fetal lactate concentrations.

Infusion of 10% dextrose led to glycosuria and an osmotic diuresis. As one of the aims of the infusion is to correct dehydration, this therapy is clearly illogical. Hypotonic solutions should also be used with caution in view of the risk of maternal and neonatal hyponatraemia (Tarnow-Mordi *et al.* 1981).

In conclusion, high-dose glucose infusion to correct ketonuria during labour appears to be unjustifiable. In addition, the administration of Hartmann's solution in large quantities should be questioned. If rehydration is necessary, normal saline is advocated. The value of administering an intravenous dextrose solution during labour is unproven but if this is considered to be necessary, physiological requirements (approximately 10 g/h) should not be exceeded.

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Platelet values during normal pregnancy

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Summary. Blood samples were obtained from 26 healthy women at regular intervals throughout pregnancy and analysed using a Coulter Counter Model S Plus III. The mean values for the various haematological indices at each stage of gestation were first calculated; the platelet count showed a small decrease throughout pregnancy as did haemoglobin concentration while there was an apparent increase in mean platelet volume, platelet distribution width and white cell count. However, analysis of the trends within patients did not always reflect these mean changes; there was considerable variation in platelet count within individuals and the apparent fall in the group as a whole was accounted for by a considerable fall in a few individuals. The assumption that the trends in platelet values determined from groups of patients will indicate how individual pregnant women behave is misleading.

Although it is generally accepted that the haemoglobin concentration decreases and white cell count increases during normal pregnancy there is less accord regarding changes in platelet count (Taylor & Lind 1976). A review of publications during the last 25 years revealed six papers reporting a decrease in platelet count during normal pregnancy (Shaper *et al* 1968; Bonnar *et al.* 1969; Sejeny *et al.* 1975; O'Brien 1976; Pitkin & Witt 1979; Fay *et al.* 1983), two papers which reported no overall change (Todd *et al.* 1965; Fenton *et al.* 1977), and one paper which reported a rise in the count (Mor *et al.* 1960). In only two of the above papers were the data obtained on a longitudinal basis but in neither of them was a within-patient analysis performed.

This longitudinal study was undertaken to determine the changes occurring in the usual platelet and other haematological indices in individual healthy pregnant women and to see how these related to the changes in the group as a whole.

Patients and methods

As part of a general physiological study blood samples were obtained from 26 healthy pregnant volunteers at about 6, 8, 10, 12, 16, 20, 24, 28, 32, 36 and 38 weeks gestation. On each occasion 20 ml of blood was taken of which 4 ml was collected into a tube containing EDTA as an anticoagulant. Not every patient could attend on each occasion: the mean number of blood samples per patient was 9·8 with a range of 7–11 samples Six patients were excluded from the final analyses of data because in the last trimester they were inadvertently given oral iron supplements and despite the small exposure to this therapy we could not exclude some possible effect. But when the data were analysed before and after the exclusion of these patients no marked differences were found.

The mean age of the patients at booking was 27 years (range 23–34 years). The mean parity

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was 0·65 (range 0–2) and the mean gestation at delivery was 39·1 weeks (range 36–41 weeks). The mean birthweight was 3·35 kg (range 2·53–4·48 kg).

Blood samples were analysed with a Coulter Counter Model S Plus III. Calibration was performed daily using the manufacturers' kit and a control sample was included with each batch of 20 blood samples. In order to test the reproducibility of the results 10 blood samples collected at widely different times during the period of the study were divided into two for duplicate analysis under blind conditions. Analysis of these duplicate pairs showed the differences to be small as reported previously (Taylor & Lind 1976). The statistical methods used were as described in Armitage (1971) and will be detailed below.

Results

Mean values for the various haematological indices, calculated for the whole group at the 11 time points during pregnancy, showed a small decrease in platelet count during pregnancy which did not achieve significance while the 'platelet crit' showed no change. Mean platelet volume had increased by the end of pregnancy and there appeared to be an increase in platelet distribution width from mid-pregnancy onwards. Haemoglobin concentration showed a significant decrease during pregnancy but mean corpuscular volume showed little overall change. The total white cell count increased progressively throughout pregnancy but the percentage of lymphocytes decreased (Table 1). To illustrate these changes the 17 patients having measurements determined at both 8 and 36 weeks gestation were analysed by paired *t*-test; the levels of significance achieved are shown in Table 1. Our data thus agree with previous reports using this form of analysis.

To use all of the data available from each patient a regression line was calculated for every haematological measurement against the day of gestation. Whether these individual indices

Table 1. Mean haematological values for the group at 11 periods of gestation

Gestation (days)	*n*	PCT ($\times 10^9$/l)	PCR (l/l)	MPV (fl)	PDW	Hb (g/dl)	MCV (fl)	WCC ($\times 10^9$/l)	Lymph %
1–49	10	290	0·24	8 49	16 56	12·70	88·91	6·35	27·10
		(91)	(0 06)	(1·09)	(0·57)	(0 89)	(2·2)	(1·64)	(7·59)
50–63	19	283	0 23	8·17	16·41	12 39	87·93	6·41	24 84
		(61)	(0·04)	(1·25)	(0·30)	(0·85)	(3·09)	(1·38)	(5·56)
64–77	18	281	0·23	8·43	16·67	12·61	88·10	6·87	23·50
		(64)	(0·05)	(1·32)	(0·67)	(0·73)	(2·78)	(1·14)	(5·20)
78–98	20	262	0·21	8·15	16·45	12·22	88·57	6·88	24·00
		(48)	(0·04)	(1·21)	(0·42)	(0·85)	(3·20)	(1·42)	(5·57)
99–126	19	269	0·22	8 27	16·45	11·95	89·38	7·19	22 11
		(61)	(0·04)	(1·26)	(0·41)	(0·95)	(3·42)	(1·27)	(5 13)
127–154	18	266	0·22	8·48	16·52	11·68	89·92	7·92	20·89
		(75)	(0·06)	(1·37)	(0·42)	(0·92)	(3·57)	(1·69)	(5·11)
155–182	20	269	0·22	8·33	16·66	11·45	90·05	8·12	20·30
		(66)	(0·05)	(1·28)	(0 34)	(0 88)	(4·33)	(1·74)	(4·66)
183–210	19	263	0 22	8·46	16·81	11·37	88·52	8·65	19·44
		(62)	(0·04)	(1·35)	(0·37)	(0·83)	(4·38)	(1·84)	(3 55)
211–238	19	270	0·22	8·55	17·05	11·17	87·19	9 15	19·79
		(62)	(0·05)	(1 57)	(0·52)	(0·85)	(5·84)	(2·23)	(3·32)
239–259	18	259	0·23	9·12***	17·44***	11·11***	85·92	8·71***	20·44**
		(62)	(0·04)	(1·57	(0·69)	(0·76)	(6·19)	(2·02)	(3·68)
260–273	16	268	0·24	8·99	17·24	11·36	85 48	8·51	21 44
		(65)	(0·03)	(1·07)	(0 64)	(0 88)	(4·49)	(1 76)	(3·61)

Standard deviation shown in parentheses.

Significant change between 8 and 36 weeks· $^{**}P<0{\cdot}01$; $^{***}P<0{\cdot}001$.

n, Number of patients in group; PCT, platelet count, PCR, platelet crit; MPV, mean platelet volume; PDW, platelet distribution width; Hb, haemaglobin; MCV, mean corpuscular volume; WCC, white cell count; Lymph %, lymphocyte percentage.

increased or decreased in value throughout pregnacy is shown in Table 2 together with the mean value for the slopes, their standard error, the t-test values and their significance (P). Group regression analysis was undertaken to determine the common slope for each haematological index. For seven of the 20 patients the platelet count increased during pregnancy though none achieved a significant slope; while the remaining 13 had a negative slope only two were significantly different from the horizontal ($P<0\cdot01$). The relation between platelet crit and gestation produced equal numbers of increasing and decreasing values of which only two of the positive slopes achieved significance at $P<0\cdot01$. Sixteen patients had a positive slope for mean platelet volume against gestation but only seven of these were significant. Platelet distribution width correlated positively with gestation in 19 of the 20 patients and 10 of these slopes attained significance at $P<0\cdot01$. Similar relations were examined between haemoglobin concentration, mean corpuscular volume, white cell count and lymphocyte percentage with gestation and the data are summarized in Table 2. These confirmed the previously reported trends such as the decrease in haemoglobin concentration and increase in white cell count. However, when the individual slopes were compared to each other and to the common slope for each haematological index they all showed significant variation indicating that while the common slope gave a guide to the general response which could be expected from a group of normal pregnant women it could not be used to indicate the extent of an individual's response throughout pregnancy.

Discussion

It has become accepted practice to undertake various laboratory tests on groups of patients and express the values in terms of a mean and standard deviation or express limits as multiples of the median with the implication that individuals will follow these mean changes While this is broadly true for some trends such as the decrease in haemoglobin or the increase in total white cell count the variation between individuals is such that even for these particular indices the mean values are poor predictors of how individuals will respond. The situation with regard to platelet changes is even less predictable. The majority of previous reports have suggested that the platelet count decreases as pregnancy progresses and the mean values for platelet counts in our data do reflect such a change. But individual patients varied, some increasing their count, other decreasing it, and some not showing any change at all, so that no generalization about change in platelet count during pregnancy can be made. Mean platelet volume increased for the group as a whole and the majority of patients showed such an increase but only seven did so at a statistically significant level and it would be misleading to claim a specific pregnancy effect. The most striking change was in platelet distribution width which, though expressed in arbitrary units, increased in the majority of patients. This probably reflects an increased platelet turnover which would support the idea that platelet survival time is decreased during normal pregnancy (Wallenburg & Van Kessel 1978).

The obstetrician is relying increasingly upon

Table 2. Within-patient regression line between the various haematological values and day of gestation

	Direction of slope				
	Positive	Negative	Mean (SE) of slopes	t	P
Platelet count	7	13	−0·072 (0·031)	2·31	*
Platelet crit	10	10	0·00002 (0·00003)	0·73	NS
Mean platelet volume	16	4	0·0036 (0·0005)	7·9	***
Platelet distribution width	19	1	0·0041 (0·0004)	11·3	***
Haemoglobin	1	19	−0·0072 (0·0005)	13·3	***
Mean corpuscular volume	7	13	−0·011 (0·002)	5·0	***
White cell count	20	0	0·012 (0·001)	12·6	***
Lymphocyte percentage	4	16	−0·024 (0·003)	7·6	***

*$P<0\cdot05$, ***$P<0\cdot001$.

laboratory tests for the management of pregnant women. Not only must there be an awareness that the 'normal' range for virtually all laboratory values will be altered and pregnancy-specific ranges need to be defined but that such ranges should be based upon longitudinal studies so that the patterns of normal individual variation can be appreciated.

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Nausea and vomiting and dietary cravings and aversions during pregnancy in South African women

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Summary. Frequency and severity of nausea and of vomiting during pregnancy, and of pronounced dietary cravings and aversions, were determined in a series of South African rural and urban black, Indian, coloured (European–African–Malay) and white women. Frequency of severe nausea ranged from 3·8% in rural blacks to 19·8% in white women, and of severe vomiting from 3·1% in rural blacks to 17·8% in white and Indian women. Proportions in the other groups were intermediate. Pronounced cravings, claimed by 67–84% in the various groups, included sour, savoury and sweet foods, also fruit and milk. Aversions were claimed by 45–81% of the women in the different groups with meat, fish, coffee and fatty foods, the foods most often avoided. Pica, the consumption of such substances as earth, clay, varied ethnically and regionally; frequency was high in rural and urban black women (44·0% and 38·3%), but much lower (5%) in Indian, coloured and white women.

Nausea and vomiting in pregnancy have been known for millenia, and were described as long ago as 2000 BC in an ancient papyrus in the Petrie collection. The symptoms, reported to affect from half to three-quarters of pregnant women, mostly between 6 and 14 weeks' gestation, appear unrelated to age or social class (Midwinter 1971), and despite much speculation, the causal factors remain obscure (Soules *et al.* 1980). Since little information is available on the experiences of non-European women, appropriate enquiries have been made on series of South African black (rural and urban), Indian and coloured (European–African–Malay), as well as white women.

Pronounced dietary likes and dislikes in pregnancy, reported to occur in two-thirds of women (Taggart 1961), have also been described from early times. They were mentioned by Soranus and by later writers such as Culpepper, who, in his *Directory for Midwives* published in 1651, referred to 'diverse longings and continual vomiting' as among the earliest signs of pregnancy (Fairweather 1968). Enquiries into the frequency, causation and significance of the phenomena, with few exceptions (Hobson 1948; Edwards *et al.* 1954; Harries & Hughes 1957; Taggart 1961; Hook 1978), have been limited. As with nausea and vomiting, there is very little information on the occurrence and frequency of strong cravings and aversions among non-Western women during pregnancy (Darwish *et al.* 1982; Sugiura *et al.* 1983). There is a similar dearth of information on the occurrence in pregnancy of pica, the consumption of non-nutritive substances such as earth, ashes, clay, chalk, starch or ice. We have therefore sought information on the phenomenon in the various racial

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groups in the Republic of South Africa: blacks, both rural and urban, Indians, coloureds and whites.

Subjects and methods

Subjects

South African constituent populations include approximately 19 million blacks, about 40% of whom live in urban areas. There are 4¼ million whites, 2½ million coloureds and ¾ million Indians; the majority of each of these three populations are urban dwellers. The women sampled in this study were:

Blacks, rural. A total of 560 women in three areas of the Transvaal where previous research investigations have been pursued; namely, in Kangwane, 275 miles east of Johannesburg; in Lebowa, 270 miles north of Johannesburg, and in Bophuthatswana, 100 miles west of Johannesburg.

Blacks, urban. A total of 412 women in middle-class areas in Soweto, Johannesburg, and also in an area adjacent to Pinetown, Natal.

Indians. A total of 318 women in middle-class areas in Lenasia and Azaadville, adjacent to Johannesburg; at Laudium, near Pretoria, and at Pinetown, near Durban.

Coloureds. A total of 225 women at Toekomsrus, Roodepoort, near Krugersdorp; and at Coronationville, Johannesburg.

Whites. A total of 256 women who resided in a number of areas in Johannesburg and in Krugersdorp.

Methods

In making enquiries, three avenues of approach were employed, using interviewers who were women teachers, Church leaders, nurses, or other responsible persons. (1) They sought information from mothers of their own acquaintance whose babies were not more than 1 year old. (2) The workers, mainly teachers, were requested during vacations to enquire into the experience of *all* appropriate mothers in specified sections of their particular areas. (3) They also made enquiries from series of women attending local antenatal, postnatal, and family planning clinics. All those questioned were happy to co-operate; none refused.

In each ethnic group the three modes of approach yielded much the same pattern of information; results were therefore combined. Moreover, since in each ethnic group the results on women in the different areas studied were closely similar, all results were combined for each ethnic group.

The questions asked included: (1) Age. (2) Total number of pregnancies. (3) Age of last child. (4) With your last pregnancy did you feel nauseous, mildly or severely, during the first 3–4 months, or throughout pregnancy? (*Mild* nausea or vomiting implies that such occurred either only mildly or only occasionally, and was not particularly distressing; *severe* nausea or vomiting implies that it occurred severely almost every day and occasionally throughout the day.) (5) With your last pregnancy did you vomit, slightly or severely, during the first 3–4 months or throughout pregnancy? (6) If you have had more than one child, what were your previous experiences of nausea and vomiting? (7) Did you experience, occasionally, or frequently, pronounced cravings (strong likes) or aversions (strong dislikes) of certain foods during pregnancy? Which foods (in order of preference) did you crave for, and which foods did you avoid? (8) If you have had more than one child, what were your cravings and aversions experiences during previous pregnancies? (9) During pregnancy did you feel urged to eat any substance not normally eaten, e.g. soil, ash, sand, chalk, starch, ice? If you did, how often, how much, and for how long did the practice continue?

In making enquiries, endeavours were made to ensure that the manner of presentation of the questionnaire was the same with all helpers in each ethnic group.

In seeking information on nausea alone, and on nausea and vomiting, and of their degree of severity, it transpired that, unfortunately, the answers obtained were less satisfactory than we had hoped, more especially in some of the rural groups studied. This was due in part to the subjective nature of the questions and to the frequent vagueness of replies.

Results

For the five inter-ethnic series of mothers studied, results on the frequency and severity of nausea, and of nausea and vomiting, of cravings and aversions, and of pica, are summarized in Tables 1 to 3.

Table 1. Percentages of South African women who experienced nausea, and nausea and vomiting, during pregnancy

	Black rural (*n* = 560)	Black urban (*n* = 412)	Indian (*n* = 318)	Coloured (*n* = 225)	White (*n* = 256)
Age (years) mean (SD)	25·8 (6·8)	26·3 (4·9)	26·6 (5·3)	25·4 (6·0)	26·1 (6·1)
Total nausea and vomiting (all grades)	55·7	57·4	68·5	61·6	64·7
Severe nausea					
0 to 3–4 months	3·2	3·4	14·4	12·5	15·2
0–9 months	0·6	0·5	4·7	3·9	4·6
Severe nausea and vomiting					
0 to 3–4 months	2·7	2·9	12·2	10·4	11·1
0–9 months	0·4	0·4	5·6	4·9	6·7

In the categories—*severe* nausea, and *severe* nausea and vomiting—the percentages affected during 0 to 3–4 months do not include the percentages of women who were affected throughout pregnancy

Table 2. Percentages of particular cravings and aversions experienced by South African pregnant women

	Black rural (*n* = 560)	Black urban (*n* = 412)	Indian (*n* = 318)	Coloured (*n* = 225)	White (*n* = 256)
Cravings % Affected	72·3	67·5	80·6	83·6	83·6
	fruit (24·3)	fruit (10·2)	'sour' foods (17·6)	fruit (64·8)	sweets and confectionery (14·1)
	cold drinks (11·8)	cold drinks (9·2)	sweets and confectionery (11·6)	cold drinks (5·7)	'sour' foods (9·3)
	fresh milk (7·1)	sour milk (maas) (7·3)	fruit (7·9)	sour milk (4·2)	fruit (6·3)
Aversions % Affected	61·2	44·7	63·3	80·5	81·3
	meat (17·3)	meat (11·4)	meat (33·6)	meat (30·2)	meat (18·7)
	tinned fish (6·3)	cabbage (6·3)	fish (6·6)	fatty foods (8·4)	coffee and tea (7·0)
	eggs (6·3)	fried foods (5·1)	cooked foods (6·3)	eggs (5·7)	fatty foods (6·2)

The total number of foods listed as liked or disliked was extremely varied, so that although some foodstuffs were very commonly mentioned their proportion constituted less than half of the total.

Nausea and vomiting

Total frequency of all grades of nausea alone, plus nausea and vomiting, ranged from 55·7% and 57·4%, respectively, in rural and urban black women to 68·5% and 64·7% in Indian and white women. The rates for black women are in line with proportions reported in a small series of rural black women of 21·6% for nausea alone,

Table 3. Percentages of South African women in 5 ethnic groups who experienced pica during pregnancy

	Black rural (*n* = 560)	Black urban (*n* = 412)	Indian (*n* = 318)	Coloured (*n* = 225)	White (*n* = 256)
% Affected	43·9	38·1	2·2	4·4	1 6
Most popular substances	soil ash	soil ash	soil clay	soil ice	chalk ice

Other substances included: clay from termite heaps (very popular with rural blacks), charcoal, plaster, egg shells, baby powder, baking powder, toothpaste, raw tobacco from cigarettes

and 30·4% for nausea and vomiting (total 52·0%) (Louw 1966). Reported proportions of total nausea and vomiting occurring among white women range from 50% to 80% (Fairweather 1968; Midwinter 1971).

Proportions for severe nausea, and severe nausea and vomiting, ranged from 3·8% and 3·1%, respectively, in rural black women, to 19·8% and 17·8% in white women.

In spite of the uncertainties mentioned, there is no doubt about the validity of the tendency of Indian, coloured and white women to have more frequent and severe nausea, and vomiting, compared with rural and urban blacks.

In all ethnic groups, the frequency of nausea and vomiting was highest in the first trimester; the proportions ranged from 77·0% with rural blacks to 85·2% in the case of the white women.

In all groups, the multiparous claimed no marked tendency for a greater frequency and severity of nausea and vomiting with the first pregnancy, although this observation has been reported by others (Midwinter 1971; Soules *et al.* 1980). Many black women insisted that the second or later pregnancy was the occasion of greater severity of sickness. However, as noted by the authors just cited, the situation was found to be variable; i.e. a woman could be very sick in one pregnancy, and yet much less affected or even not affected at all in a previous or in a subsequent pregnancy. This was especially the case with black women.

Of the blacks studied, 24 had had twins; 18 of them maintained that they were 'very sick' in that pregnancy; in five of the 18 the sickness was distressing throughout pregnancy. This experience of greater sickness has also been reported for white mothers of twins (Midwinter 1971; Soules *et al.* 1980).

Cravings and aversions

Cravings. The proportions of women who reported pronounced cravings ranged from 67% with urban blacks to 84% with whites. Proportions reported for white women elsewhere range from 40% to 80% (Harries & Hughes 1957; Taggart 1961; Hook 1978; MacIntyre 1983). Cravings were most intense in the first trimester. Of women affected, a large proportion, 59–72%, stated that their likes and dislikes, although irregular and of variable intensity, persisted throughout pregnancy. Furthermore, a small number (<2% in each ethnic group) maintained that their strong cravings during pregnancy persisted, although with less intensity, after parturition. As to the foodstuffs involved (Table 2) the pattern of cravings, was much the same for the South African groups as that described in published studies on white women; namely, there were enhanced desires for sour, savoury and sweet foods, and fruit. They concerned food components within the range of their everyday diets. The black women principally desired more fruit, which is fairly readily available seasonally, in the rural areas, although less so in urban centres where it is increasingly expensive. The increased desire for milk was for a food not consumed every day. The desire for cold or carbonated drinks was a real craving, and not simply a thirst quencher since these drinks are expensive especially to the less privileged. As comparison in a series studied in Yokohama, Japan, the diet of 45% of women changed, the preference being for 'sour and rich dishes' (Sugiura *et al.* 1983)

Pica. The proportions given in Table 3 relate to *regular* ingestors of alien substances. Proportions were higher if irregular consumers were included. While the practice did occur among white women, it was rare. Yet nearly half of both rural and urban blacks were affected; i.e. similar to the experience of predominantly black women studied in a region in rural Mississippi, USA (Vermeer & Frate 1979). In each ethnic group a variety of substances were eaten. The amounts consumed daily varied from 5 g to about 50 g, but in one region in Eastern Transvaal far larger amounts (of earth) were claimed to be eaten regularly by pregnant black women. In the study made in rural Mississippi, geophagia (the eating of earth) was reported to occur among 57% of women and 16% of children of both sexes; the average daily consumption was 50 g. Somewhat similar amounts were indicated by Halstead (1968), and in South African blacks by Sayers *et al.* (1974). However, in the investigations of Roselle & Englewood (1970) on black women in New York, starch and clay were consumed in far larger amounts, which varied from 250 g to 1300 g daily. As to the time of day when pica occurred, almost all women affected in the different ethnic groups said that they simply ate when they felt the urge. About a fifth ate after a meal. In the study made in Mississippi a third ate clay after meals.

Aversions. Frequencies of pronounced dislikes (Table 2), which ranged from 44·7% in urban black women to 81·3% in white women, were similar to the proportions reported in the literature. Broadly, the foodstuffs avoided were the same or similar to those reported in the case of white women (Taggart 1961; Hook 1978). In brief, among those affected there were dislikes, or much reduced consumptions, of tea, coffee, meat (whether boiled or fried), fish, fatty and oily foods. In the case of the rural blacks the restriction of meat concerns a food of which apart from pregnancy they would certainly wish to eat more. The same applies to the avoidance of tinned fish—an increasingly popular and relatively inexpensive food the consumption of which is rising rapidly. As a comparison, in a study in Iraq, 15% of women avoided spices; moreover, 31% avoided melons, onions, leeks, radishes and fish. Interestingly, these foods were avoided by half of the mothers during lactation (Darwish *et al.* 1982).

Discussion

Significance of cravings

Hytten & Leitch (1964) suggested that cravings may be due to a dulling of the sense of taste in pregnancy. It is remarkable that this probability has not been seriously investigated, bearing in mind the large number of intensive studies published on taste sensitivity and disease; e.g. sweet taste sensitivity in relation to caries (Catalanotto *et al.* 1979), obesity (Grinker 1978) and diabetes (Lawson *et al.* 1979); and salt taste sensitivity in relation to elevated blood pressure (Pangborn & Pecore 1982).

Although it is plausible to associate changes in food habits in pregnancy as being evoked, consciously or unconsciously, to meet increased physiological needs of particular nutrients—this view is regarded as unproved (Taggart 1961; Halstead 1968; Hook 1978; Vermeer & Frate 1979). In the case of geophagia, while the practice may contribute significant amounts of calcium and trace elements, under certain conditions it may exacerbate an existing iron deficiency anaemia. The extent to which iron deficiency causes geophagia, or geophagia promotes iron deficiency is not wholly clear, but the evidence of Coltman (1969) and Crosby (1976, 1982) strongly favours the former view. From their studies on blacks in Soweto, Johannesburg, Sayers *et al.* (1974) concluded that 'the eating of local earth and ashes cannot have a deleterious effect on iron nutrition in the vast majority of cases'.

For pica there are no clear-cut explanations. In the USA, Vermeer & Frate (1979) concluded that 'Geophagia in the black community . . . represents a common custom stemming from deeply-imbedded cultural traditions and attitudes. While it appears to arise from no discernible nutritional needs, it has implications for health and well-being'. The same generalization applies to South African black women, and also in measure to Indian and coloured women. Clearly, as Reid & Taylor (1979), Worthington-Roberts (1984) and others have maintained, there is much concerning the aetiology and medical implications of pica that remain unresolved.

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Fetal umbilical artery flow velocity-time waveforms in twin pregnancies

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Summary. The umbilical artery flow velocity-time waveforms were studied in 76 twin pregnancies. The ratio of peak systolic (A) to least diastolic (B) velocity was calculated for each fetus as an index of umbilical placental flow resistance. Seventy-one sets of twins were studied within 14 days before delivery. In 65 cases both twins were alive at the time of study. In 32 pregnancies both fetuses were of birthweight appropriate for gestational age (AGA) and had A/B ratios within the normal singleton range. In 33 pregnancies one or both of the liveborn infants were small for gestational age (SGA) and in 78% of these at least one fetus had an elevated A/B ratio. Discordancy in birthweight and A/B ratio was associated with growth retardation. Clinically manifest twin-to-twin transfusions occurred in five of the ten pregnancies resulting in an SGA infant (eight with discordant weight) associated with a normal and concordant A/B ratio. Two twin-to-twin transfusions were associated with perinatal death. The placentas were examined in 61 patients. In 43 dichorionic pairs the A/B ratio was elevated in 12 of the 18 where there was at least one SGA infant. There was a greater incidence of growth retardation in the monochorionic pairs (12 of 18). Only seven of these were identified by an elevated A/B ratio. In 10 of these 18 pairs vascular anastomoses were demonstrated on placental inspection and in a further two there was evidence of twin-to-twin transfusion by haemoglobin discrepancy. Twin pregnancy may result in the birth of a small-for-dates infant because of intrauterine growth retardation or twin-to-twin transfusion. An abnormally elevated A/B ratio identifies growth retardation. In twin-to-twin transfusion the A/B ratio of the two fetuses is similar (crossed circulation) yet difference in size may be seen on ultrasound measurement.

Umbilical artery flow velocity-time waveforms provide a measure of fetal placental blood flow resistance and so an index of flow (flow = pressure/resistance). In the singleton pregnancy low diastolic blood flow velocity in the umbilical circulation is indicative of high fetal placental blood flow resistance and is seen in association with fetal growth failure (Trudinger *et al.* (1985*a*). A characteristic placental microvascular lesion with obliteration of the small arteries and arterioles of the tertiary villi has been demonstrated in association with this antenatal measure of increased blood flow resistance (Giles *et al.* 1985). In a study of fetal umbilical and maternal uterine artery flow velocity wave-

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forms only some cases of fetal growth retardation and high umbilical artery resistance were seen to be associated with high resistance in the maternal uterine circulation (Trudinger *et al.* 1985*b*). Twin pregnancies provide a situation in which two fetuses usually share the same utero-placental circulation and for monozygotic twins identical genetic potential but usually have a discrete umbilical placental circulation. It thus provides a well-controlled situation to relate fetal growth to Doppler studies of the umbilical placental circulation. Discordancy in fetal growth and welfare in twin pregnancies is notoriously difficult to recognize (Neilson 1981). A part of the increased perinatal mortality associated with twin pregnancy (Hawrylyshyn *et al.* 1982) is attributable to intrauterine growth failure in addition to premature labour (O'Connor *et al.* 1981) and other problems (McCarthy *et al.* 1981). In this study the umbilical artery waveforms of the two fetuses of a twin pregnancy were related to fetal growth.

Patients and methods

Seventy-six patients with twin pregnancies were studied on 260 occasions (mean = 3·4, range 1–12). In 71 patients the last study was within 14 days of delivery (61 within 7 days of delivery). This group was studied on 254 occasions (mean = 3·6). These were a consecutive group followed at two week intervals from 28 weeks. If fetal compromise (abnormal ultrasound or abnormal fetal heart rate monitoring) was suspected studies were more frequently performed.

A B-mode linear array real-time ultrasound scan was carried out to determine the position of each fetus and a loop of umbilical cord was located. The umbilical artery flow velocity-time waveform was recorded using a continuous wave directional Doppler ultrasound velocimeter (Sonicaid, Vasoflo) with real-time spectral analysis of the directional Doppler signals as described previously (Trudinger *et al.* 1985*a*). To identify the twin under study the fetal heart motion was observed with the real time scanner and matched with the audible umbilical artery flow velocity-time waveform. The ratio of peak systolic (A) to least diastolic (B) velocity was measured in five fetal cardiac cycles in the absence of fetal breathing movements. As described previously the A/B ratio is an angle-independent index of the umbilical placental blood flow resistance (Trudinger *et al.* 1985*a*).

Cord blood was collected into an EDTA tube at the time of delivery from the umbilical vein and processed by Coulter Counter. The placenta was labelled at the time of delivery to identify the umbilical cord of each twin. If a fused placenta was present and the twins were of the same sex, the placental vasculature was injected with milk to detect any twin–twin anastomoses (Coen & Sutherland 1970). The placenta was fixed in 10% formalin in saline and examined histologically to determine whether it was monochorionic or dichorionic.

Results

The results from the patients studied are shown in Table 1. There were eight stillborn infants (from seven twin pairs). There was one longstanding fetal death (fetus papyraceous) and one intrapartum death (cord prolapse). Of the other six stillbirths one infant was an acardiac acephalic monster, this case has been reported elsewhere (Simpson *et al.* 1983). Two of the remaining stillbirths were from the same twin pair at 36 weeks gestation, on postmortem examination there was evidence of a twin-to-twin transfusion (Rausen *et al.* 1965; Galea *et al.* 1982) one of this pair was congested and the other was pallid. In the other three cases fetal death was unexpectedly discovered at the time of Doppler study 1–5 weeks before delivery. Of the six twin pregnancies with only a single liveborn infant, three of these survivors were small for gestational age (one died in the neonatal period from congenital heart abnormalities). There were five neonatal deaths including the infant mentioned above, two infants born prematurely who died of severe hyaline membrane disease, an anencephalic and an infant with Down's syndrome who died following acute septicaemia. There were no other major congenital abnormalities present amongst this group of twin pregnancies.

Of the 71 twin pregnancies delivered within 14 days of the last study there were 32 in which both

Table 1. Pregnancy outcome in the total patients studied

Total twin sets	76*
Like sex sets	58
Unlike sex sets	17
Live births	144
Stillbirths	8

* Sex intermediate in one pair with fetus papyraceous

infants had a birthweight appropriate for gestational age using singleton tables (Tanner & Thomson 1970). The umbilical A/B ratio of the two fetuses in these twin pregnancies when compared with our normal limits for A/B ratios during the third trimester (Trudinger *et al.* 1985*a*) showed close agreement with the singleton pregnancy results (Fig. 1). One of these fetuses died after cord prolapse in labour.

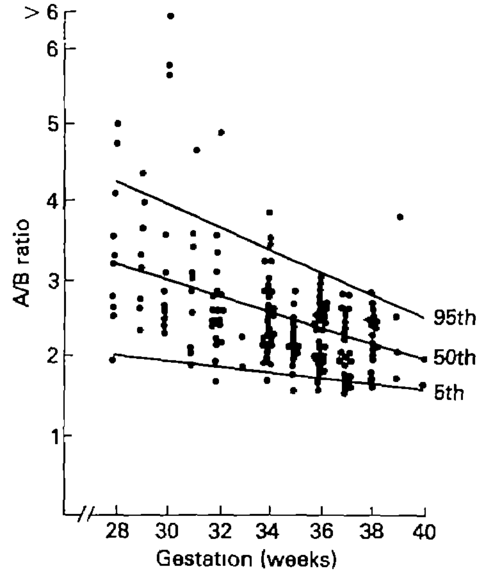

Fig. 1. Fetal umbilical artery A/B ratios in 32 twin pregnancies resulting in both infants with birthweights appropriate for gestational age. The normal limits for singleton pregnancy are shown (Trudinger *et al.* 1985*a*).

There were 64 twin pairs studied within 14 days of delivery and yielding two livebirths. The last study A/B ratios of these twin pairs are shown in Fig. 2. There were 33 pregnancies in which one ($n = 26$) or both ($n = 7$) infants were born small for gestational age (SGA). Of these 33 pregnancies 20 had one and three had two abnormal A/B ratios on the last study before delivery. One of them is illustrated in Fig. 3. In 10 pregnancies the A/B ratios of the umbilical artery waveforms of both twins were normal yet an SGA infant was born. In five of these ten patients there was evidence of twin-to-twin transfusion. In two patients there was demonstrable twin-to-twin transfusion syndrome with haemoglobin differences of >5 g/dl and/or marked plethora in one twin's placenta and pallor in the other placenta. In the other three patients twin-to-twin anastomoses could be demonstrated when the placenta was injected. The remaining five had otherwise unremarkable twin pregnancies. Evidence of twin-to-twin transfusion was also noted in the twin pregnancy containing the acardiac monster and the twin pregnancy with the double intrauterine death.

The percentage weight difference (Tan *et al.* 1979) was compared with the difference in the A/B ratios between the twins of each of the 65 pairs (including the pair with one twin dying from cord prolapse) studied within 14 days of

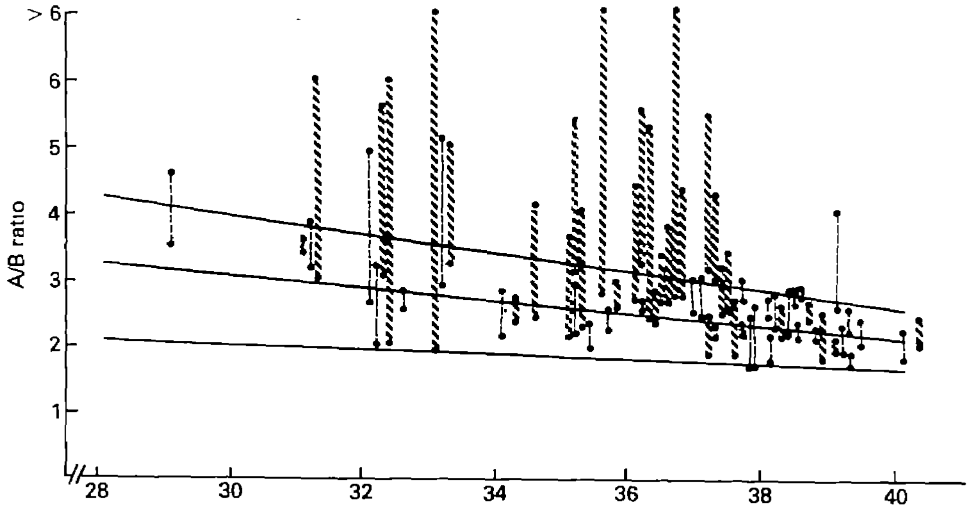

Fig. 2. The last A/B ratios for 65 twin pregnancies including the set of twins with the first twin dying following intrapartum cord prolapse. The twin pregnancies where both infants were appropriate for gestational age (dashed bars) or where one or both were small for gestational age (striped bars) are shown.

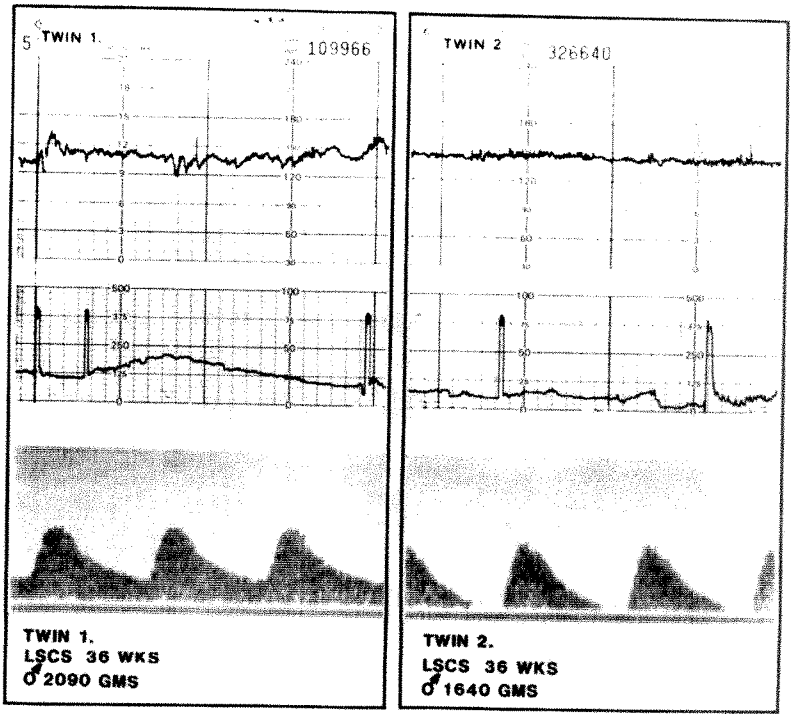

Fig. 3. The umbilical artery velocity-time waveforms and cardiotocographs from a pregnancy ending at 36 weeks demonstrating the disparity between the birthweights, cardiotocographs and umbilical artery velocity-time waveforms.

delivery. For each the differences were ranked and the third quartile values determined giving a percentage weight difference of 16·9% and an A/B ratio difference of 1·57 (Fig. 4). There were 41 patients who had values within normal limits for both variables. Of the 16 patients with an A/B ratio difference in the fourth quartile, 14 gave birth to at least one SGA infant. Significantly only 11 of the 49 patients with a 'normal' A/B ratio difference gave birth to an SGA infant (χ^2, $P<0{\cdot}001$). There were eight patients in whom the A/B ratio did not differ but the percentage weight difference was in the fourth quartile. This group included the two patients with twin-to-twin transfusion and the three with demonstrable twin-to-twin vascular anastomosis. In the remaining three patients their placentas were not injected. A further patient with twin-to-twin transfusion, proved by haemoglobin difference, also had no A/B ratio difference with a percentage weight difference of 16% (just within the normal limits of the third quartile). It is interesting that the birthweights were discordant in all but one patient where a twin-to-twin transfusion was shown to exist.

There were 10 infants with a 5-min Apgar score of <7 born in eight pregnancies. In one pregnancy the other twin was stillborn. In five of the remaining seven pregnancies the A/B ratio difference was in the fourth quartile.

Sixty-one placentas were reviewed histologically, 18 (30%) were monochorionic and 43 (70%) were dichorionic. The effect of type of placentation on the twin pair centile and comparative birthweights and A/B ratio differences are shown in Table 2. Of the 18 monochorionic placentas, 10 (56%) showed demonstrable vascular communications between the circulations on injection of the placentas. These 10 twin pairs included the pair in whom both twins died *in utero* at 36 weeks and the pair with one twin an acardiac acephalic monster. Of the eight remaining twin pairs there were two pairs with twin-to-twin transfusion syndrome diagnosed by marked haemoglobin discrepancy (the third case of twin-to-twin transfusion did not have placental injection studies), three pairs with marked weight discordancy and three pairs with neither of these features. Of interest is the similarity in the incidence of A/B ratio difference for both monochorionic and dichorionic twin pairs. This paradox is accounted for by the occurrence of

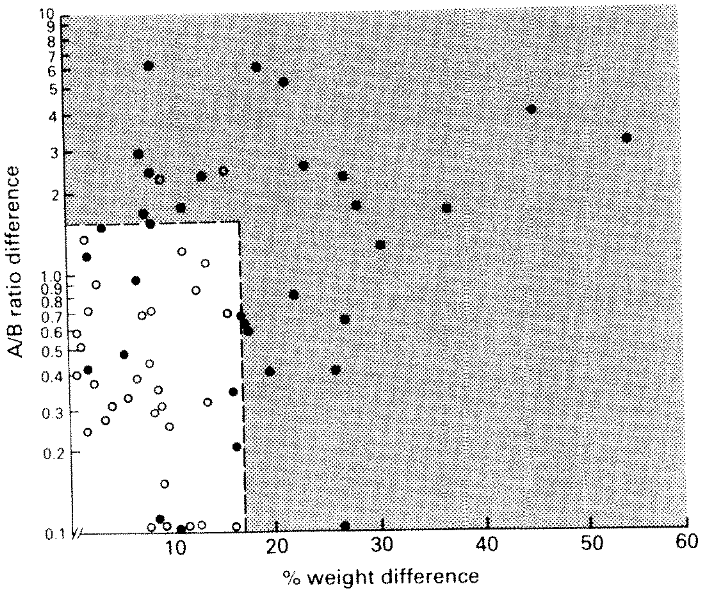

Fig. 4. The last study A/B ratio difference and percentage weight difference between the twins of 65 twin pairs. The 75th centiles for both parameters are shown (A/B difference—1·57, percentage weight difference—16·9%). ○ Both twins appropriate weight for gestation; ●, one or both twins small for gestation.

discordant fetal growth in the patients with twin-to-twin transfusion which were confined to the monochorionic placenta group and exhibited no A/B ratio difference.

Forty-four of the twin pregnancies had ultrasound measurements of biparietal diameters (BPD). Twenty-one pairs were examined within 14 days of delivery; in seven there was a disparity of ≥6 mm and four of these showed discordancy of weight. Of the six patients with a BPD disparity of 3–5 mm only two had discordant weights and of the eight with a BPD disparity of ≤2 mm, one set of twins had discordant weights.

Discussion

The growth rate of twin fetuses has been reported to fall behind that of a single fetus at or about 30 weeks gestation (McKeown & Record 1952; Naeye *et al.* 1966). Twin fetuses up to that

Table 2. The effect of type of placentation on liveborn twin pair birthweights

	Placentation	
	Dichorionic	Monochorionic
Total liveborn twin pairs (*n*)	42	15
Comparative birthweight		
Concordant (*n*)	34	7 ($P<0{\cdot}001$)*
Discordant (*n*)	8	8
Centile birthweight		
Both twins ≥10th centile	24	3 ($P<0{\cdot}001$)*
One or both twins <10th centile	18	12
A/B ratio difference (>75th centile)		
Absent	30	12 (NS)
Present	12	3

*χ^2 test.

gestation are identical in size to singleton fetuses of the same gestation (Gruenwald 1966). This suggests a limit to the growth support that can be provided by the uteroplacental circulation. Beyond this limit there is growth failure (or retarded growth). Our results show that those pregnancies resulting in the birth of two fetuses of birthweight appropriate for gestational age (using singleton tables) had normal umbilical artery flow velocity-time waveforms. The A/B ratio, an index of peripheral (or placental) resistance and thus flow, was also normal (again relative to our singleton pregnancy studies). In contrast, in those pregnancies resulting in the delivery of an SGA infant the umbilical artery flow velocity waveforms exhibited low diastolic flow velocities and a high A/B ratio consistent with increased fetal placental flow resistance and reduced flow in pregnancies not associated with twin-to-twin transfusion. In this group there was a large difference in the A/B ratio of the individual waveforms from the twin pair. Discordant fetal size implies a discrepancy in growth rate at least over the final trimester. Since it is the same uteroplacental bed then limitation on growth support must result from unequal sharing of uterine blood flow. Hence the changes in the umbilical artery flow velocity time waveforms and the implied change in resistance and thus flow are secondary to this uterine disparity as the fetuses otherwise share the same environment and in monozygous twins identical genetic constitution.

The study method allowed confident recording of the umbilical artery waveforms of the two fetuses of each pair antenatally. However, the individual twin fetuses could not be identified at birth so that antenatal studies were analysed in terms of the twin pair and their dissimilarity. In many pairs we felt confident but could not be certain that the small fetus had the abnormal umbilical artery waveform.

The long-term effects of intrauterine growth failure in twins where there has been a difference of >25% between fetal weights have been reported by Babson *et al.* (1964) and Babson & Phillips (1973). They report a long-standing effect on the growth and intelligence of the smaller twin. Our studies of the umbilical artery velocity-time waveform allows the antenatal identification of the twin developing growth failure in 70% of patients (23 of the 33 pairs with one or both twins small for gestational age were recognized by an abnormal study). Our results compare favourably with those reported by Houlton (1977) for the ultrasound diagnosis of the twin fetus small for gestational age. Houlton (1977) reported that with a difference in BPD of between 3–5 mm, 40% of the twins were SGA, and with a difference of ≥6 mm, 71% of the twins were SGA. Haney *et al.* (1978) also reported a disparity of >6 mm in BPD was associated with poor neonatal outcome. Comparative analysis of our results shows that the A/B ratio has a predictive value of 70% (23/33) and a specificity of 70% (23/33) in the diagnosis of the SGA twin (Table 3). As measurements of the A/B ratio are performed in conjunction with real-time ultrasound it may be possible to determine which twin is in fact compromised. Therefore, if the second twin is believed to be compromised and delivery is thought to be necessary, lower-segment caesarean section may be more appropriate as the second twin is more difficult to monitor during labour.

A surprise finding in this study was that eight sets of twins, although showing a disparity in birthweight greater than the normal, had no

Table 3. Comparative analysis of twin assessment for A/B ratio and ultrasound analysis of BPD difference

		Ultrasound BPD disparity[*] (mm)	
	A/B ratio	3–5	≥6
Sensitivity $\left(\frac{TP}{TP+FN}\right)$	23/33 70%	8/12 67%	10/18 56%
Predictive value (pos) $\left(\frac{TP}{TP+FP}\right)$	23/32 72%	8/20 40%	10/14 71%
Predictive value (neg) $\left(\frac{TN}{TN+FN}\right)$	23/33 70%	18/22 82%	30/38 79%
Specificity $\left(\frac{TN}{TN+FP}\right)$	23/32 72%	18/30 60%	30/34 88%

[*] Data from Houlton (1977) of 28 patients studied serially

TP, true-positive, TN, true-negative, FP, false-positive, FN, false-negative corresponding disparity in the A/B ratios. In two of these sets of twins, twin-to-twin transfusion was proven by a haemoglobin disparity of >5 g/dl and in three other sets vascular communications between the two twins were demonstrated. In a further patient where both fetuses died before birth, postmortem study of the fetuses showed evidence of a twin-to-twin transfusion. The other three placentas were not collected for injection. Our incidence of twin-to-twin transfusion syndrome of 28% (i.e. five of 18 monochorionic twin pairs) is similar to that quoted by Falkner (1978) who reported an incidence of twin-to-twin transfusion of 30% of monochorionic twins. Other reported incidences of twin-to-twin transfusion in monochorionic twins have varied from 15 to 30% (Rausen *et al.* 1965; Sekiya & Hafez 1977; Fox 1978). Wittman *et al.* (1981) differentiated between ultrasound disparity in twin pregnancy as being due to twin-to-twin transfusion in the second trimester and intrauterine growth retardation in the third trimester. Our experience does not support this differentiation as the twin-to-twin transfusions we report occurred in the third trimester. We believe that twin-to-twin transfusion may be strongly suspected if a discrepancy in ultrasound size is seen in the presence of no A/B ratio difference. This explains the apparent paradoxical finding of the increased occurrence of SGA infants and discordant weights in monochorionic twin pairs with no increase in the incidence of A/B ratio difference. Our proposed method of diagnosing significant twin-to-twin transfusion is more easily applied than that described by Brennan *et al.* (1982) who reported five diagnostic ultrasound features of the syndrome in a set of twins. Both their twins, however, were growth retarded when born at 37·5 weeks gestation.

Continuous-wave Doppler ultrasound is an appropriate method of assessing twin pregnancies, which avoids unnecessary admission to hospital in the uncomplicated twin pregnancy (McGillivray 1975). The at-risk twin pregnancy can be detected and dealt with, and the twin pregnancy complicated by a twin-to-twin transfusion may be more readily identified when combined with careful ultrasound assessment of fetal size.

Acknowledgments

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Single-dose amoxycillin in the treatment of bacteriuria in pregnancy and the puerperium—a controlled clinical trial

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Summary. Ninety obstetric patients with significant bacteriuria were treated randomly with either a single dose of 3 g amoxycillin or with a conventional course of ampicillin over 7 days. Treatment groups were comparable in terms of age, gravidity and socioeconomic status, and the outcome of pregnancy in the two groups did not differ significantly. Cure rates, assessed at 1 week and 6 weeks after treatment, were not significantly different: 88% for single-dose treatment and 84% for conventional treatment. It is concluded that a single dose of 3 g amoxycillin is a safe, effective and acceptable treatment for bacteriuria in pregnancy and the puerperium.

Bacteriuria in pregnancy represents a significant risk to both mother and fetus (McFadyen *et al.* 1973; Naeye 1979) and there is general agreement that prompt antibiotic chemotherapy is required to reduce these hazards (McFadyen 1980). What is not clearly established is for how long and in what dosage such antibiotic chemotherapy should be given (Greenwood & O'Grady 1977; Greenwood *et al.* 1980; Philipson 1983).

In the treatment of bacteriuria in non-pregnant women, both short courses of antibiotics (Charlton *et al.* 1976; Rapoport *et al.* 1981) and single-dose antibiotic therapy (Asscher 1981) have been found to be safe and effective. Single-dose therapy has obvious advantages in terms of patient compliance, minimization of adverse effects and financial savings (Lacey 1981; Rubin *et al.* 1980; Souney & Polk 1982). Table 1 details some recent studies suggesting that single-dose antibiotic therapy may be effective in the treatment of bacteriuria in pregnant women. As none of these studies included adequate controls it is possible that an element of bias was inadvertently introduced. Our study was therefore designed to test the hypothesis that single dose antibiotic chemotherapy of bacteriuria in pregnancy is as effective as a conventional 7-day course in populations with similar obstetric characteristics.

Subjects and methods

Patients

During a 17-month period all obstetric patients showing bacteriuria in a carefully-taken fresh mid-stream urine (MSU) specimen, where the isolate was proven to be ampicillin sensitive, were approached for inclusion into the trial. The patient population was of British nationality and was recruited from the wives of servicemen and entitled United Kingdom personnel based with the British Forces Germany. Urine specimens were obtained routinely from all patients attend-

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Table 1. Single-dose treatment of bacteriuria in pregnancy

Author	No. of subjects	Drug dosage	% cured
Williams & Smith (1970)	71	Sulphadoxime 2 g oral	52
	24	Sulphamethopyrazine 2 g oral	62
	21	Streptomycin 1 g i.m.	43
	47	Sulphamethopyrazine 1 g oral with Streptomycin 1 g i.m.	70
Bailey (1970)	12	Nitrofurantoin 100 mg oral	50
Brumfitt *et al.* (1970)	25	Cephaloridine 2 g i.m.	52
Reeves (1975)	76	Sulphamethopyrazine 2 g oral (uncontrolled)	68
	45	Sulphamethopyrazine 2 g oral (controlled against conventional duration therapy as below)	67
	37	Sulphamethopyrazine 2 g oral on day 1 and day 4–5	73
	34	Sulphadimidine 1 g four times daily for 7 days	50
Ronald *et al.* (1976)	39 No. pregnant not stated. Infection localized to bladder.	Kanamycin 500 mg i.m	92
Harris *et al.* (1982)	24	Ampicillin 2 g oral plus Probenemide 1 g oral	71
	20	Cephalexin 2 g oral plus Probenemide 1 g oral	55
	22	Nitrofurantoin 200 mg oral	73
	20	Sulphasoxazole 2 g oral	75
Campbell-Brown & McFadyen (1983)	10 Indian	Cephalexin 3 g oral	100
	27 Indigenous	Cephalexin 3 g oral	59

ing the booking, antenatal clinics at 28 and 36 weeks as well as from the postnatal ward on the 3rd day after delivery. When clinically indicated, additional MSU specimens were obtained from pregnant patients by the general practioner or obstetrician. Patients with bacterial pyelonephritis, or giving a history of hypersensitivity to β-lactam agents or who reported taking a course of antibiotics within 2 weeks were excluded.

Ethical approval for the trial was given by the Medical Research Co-ordinating Committee of the Royal Air Force.

After informed consent had been obtained the patients were allocated by computer randomization to receive either a sachet of 3 g amoxycillin prescribed to be taken last thing at night with milk, or a 7-day course of ampicillin, 500 mg to be taken every 6 h. Conventional ampicillin therapy, rather than a prolonged course of amoxycillin, was chosen as this was our hospital's existing standard treatment The treatment allocation was made by the antenatal clinic secretary so that neither obstetrician nor microbiologist was aware of the management until the 6-week follow-up visit. At the time treatment was prescribed, the patient received instructions to submit a further MSU to the laboratory 1 week after treatment and was also asked to attend the antenatal clinic 6 weeks after treatment, when a further MSU was taken and the patient was questioned about any possible drug-associated side-effects

Persistent infection, relapse and reinfection were managed along conventional lines following consultation between the investigators. After inclusion in the trial all antenatal patients were followed up in the standard manner and note was taken of the course and outcome of their pregnancy.

Microbiological methods

Bacteriuria was assessed by a semi-quantitative CLED plate technique (Association of Clinical Pathologists 1973). Isolates were identified and typed by standard microbiological methods. Antibiotic sensitivity testing was performed by Stokes method (Garrod *et al.* 1981).

Bacteriuria was defined as the detection by quantitative urine culture of at least 100 000 colony-forming units per ml of freshly voided urine. Where this was accompanied by dysuria and frequency of micturition by day and night, with or without pyuria and haematuria, the patient was diagnosed as suffering from symptomatic bacterial cystitis. Loin pain, tenderness and pyrexia were taken to be indications of upper urinary tract involvement (Report by Members of the Medical Research Council Bacteriuria Committee 1979).

Statistical analysis

The χ^2 test was employed to assess the test data from the comparative study between the two treatment regimens. The criteria employed were that a difference of ≥10% between the two treatment group failure frequencies should be detected, if it in fact existed, at a significance level of $P = 0{\cdot}05$.

Considerations of trial size and the associated power (1–β error) of the test statistic to detect the difference specified as clinically important were subject to the absolute constraint of a limited trial period. We were not in a position to predict the number of patients presenting as suitable for inclusion in the trial. However, we have examined the β error of the test statistic retrospectively, using standard formulas, (Schwartz *et al.* 1980) to make clear the relation between our data and our conclusions.

Results

A total of 5472 antenatal and 1114 postnatal specimens were screened for bacteriuria and 3·3% of the antenatal and 4·5% of the postnatal urines were found to be positive (P=0·05). The rates of recorded urinary contamination during collection were 6·8% and 16·7% respectively (P<0·001).

Of 102 patients enrolled in the trial 90 completed the protocol. Of the remainder one patient was withdrawn from the trial due to severe gastrointestinal upsets on the third day of ampicillin therapy and the rest failed to complete the protocol. The characteristics of the patients treated in both groups are described in Tables 2–4. Both treatment groups are seen to be comparable in terms of the principle obstetric determinants i.e. age, parity and socioeconomic

Table 2. Obstetric determinants of trial groups

	Single dose (n = 52)	7-day course (n = 38)
Age (years), Median (range)	24 (18–37)	25·5 (19–40)
Parity		
1	22	11
2	16	13
3	8	7
4	6	7
Socioeconomic status*		
Officer	3	3
NCO	31	25
Airman/private	18	10

* Assessed by husband's rank, NCO is a non-commissioned officer.

Table 3. Clinical status of patients at entry to trial

	Single dose	7-day course
Antenatal, asymptomatic	39	23
Antenatal, symptomatic	6	4
Postnatal, asymptomatic	7	11
Total	52	38

Table 4. Antenatal patients—gestation at entry and outcome of pregnancy

	Single dose	7-day course
Gestation at entry (weeks)	26 (6–41)	18 (9–37)
Gestation at delivery (weeks)	40 (38–41)	40 (35–41)
Birthweight (kg)	3·46 (2·59–4·4)	3·48 (1·57–4·04)

All values are presented as median with range in brackets.

status. There was no difference between the two groups in terms of gestation at entry to the trial or in terms of pregnancy progress and outcome. Finally no differences were found between the groups in respect of gestation at delivery and birthweight. The majority of patients in both treatment groups were asymptomatic.

Table 5 identifies all isolates detected during the trial period and records the number of organisms found to be resistant to the antibiotics tested. The organisms treated in the two groups were found to be of similar distribution and no pattern could be identified in the organisms associated with treatment failure (Table 6).

The results of the comparative study are shown in Table 7. Reinfections within the 6-week period were treated as antibiotic successes for statistical analysis. There were no statistically significant differences between the treatment regimens ($P = 0{\cdot}56$). The calculated β error for the trial size is 0·64.

Analysis of the combined responses to single- and multiple-dose treatments in the clinical groups antenatal/asymptomatic, antenatal/symptomatic and postnatal revealed no significant difference between the cure rates (Table 8) (Fisher's exact probability test $P = 0{\cdot}58$).

All six treatment failures in the single-dose

Table 5. Urinary infection bacterial isolates from obstetric patients investigated during the trial period with antibiotic resistances shown

Organism	No of isolates	No. of resistant isolates						
		AP	CRD	SMX	TM	NI	NA
Escherichia coli	138	39	17	60	12	15	6
Klebsiella pneumoniae	28	28	0	16	7	21	1
Group D streptococci	22	0	21	22	15	2	22
Proteus mirabilis	15	2	3	10	8	13	1
Group B streptococci	9	0	1	4	3	0	9
Staphylococcus saprophyticus	7	0	0	3	3	1	7
Enterobacter cloacae	5	2	3	0	1	4	2
Klebsiella oxytoca	4	3	1	1	0	1	0
Totals (percentages in brackets)	228	74 (33)	46 (20)	116 (51)	49 (22)	57 (25)	48 (21)

AP, Ampicillin; SMX, sulphamethoxazole; NA, nalidixic acid; CRD, cephalexin; TM, trimethoprim; NI, nitrofurantoin.

Table 6. The distribution of bacterial isolates treated in relation to outcome of management

Organism	Single-dose treatment		Multiple-dose treatment	
	Cured	Failed	Cured	Failed
Escherichia coli	33	4	22	5
Group D streptococci	7	1	4	0
Proteus mirabilis	3	1	4	0
Staphylococcus saprophyticus	2	0	2	0
Group B streptococci	1	0	0	1
Totals	46	6	32	6

Table 7. Results of comparative treatment study

	Single dose	7-day course	Totals
Cured (Reinfections in brackets)	46 (5)	32 (5)	78
Failed	6	6	12
Totals (Percentage cure in brackets)	52 (88)	38 (84)	90 (87)

$\chi^2 = 0{\cdot}34$

Table 8. Treatment response by clinical status

Clinical status	Single dose	Multiple dose	Total
Antenatal asymptomatic			
Cured	33	20	53
Failed	6	3	9
Antenatal symptomatic			
Cured	6	3	9
Failed	0	1	1
Postnatal			
Cured	9	7	16
Failed	0	2	2

treatment group were detected at the initial check MSU whereas all six failures in the multiple-dose treatment cohort were not diagnosed until the 6-week MSU specimen was analysed. (Fisher's exact probability test $P = 0{\cdot}002$).

Discussion

Many clinical trials have demonstrated the value of single-dose antibiotic treatment for bacteriuria in women (Souney & Polk 1982), children (Wallen *et al.* 1983) and the elderly (Lacey 1981), but there are few studies into this form of treatment in pregnancy (Table 1). None of these studies has contained populations controlled for the important obstetric variables of age, parity and socioeconomic status. Furthermore, with one exception (Reeves 1975), these reports have not been controlled against treatment of conventional duration. It is therefore possible that separate and distinct obstetric populations have been examined and we agree with Souney & Polk (1982) that further controlled trials are required to determine the validity of these findings.

Many of the single-dose regimens previously studied would not now be considered suitable first-line choices for covert bacteriuria in pregnancy. We, therefore, decided to evaluate amoxycillin which has been found to be successful in single-dose treatment of bacteriuria in men, non-pregnant women and children (Anderson *et al.* 1979; Bailey & Abbott; Fang *et al.* 1978;; Harbord & Gruneberg 1981; Leigh *et al.* 1980, Rubin *et al.* 1980) with very few exceptions (Avner *et al.* 1983). In addition Brumfitt *et al.* (1982) have demonstrated that, in bacteriuria in pregnancy, two doses of 3 g amoxycillin taken 12 h apart are as effective as a 7-day amoxycillin course. Since this agent has not been previously tested in a single dose against urinary tract infection in pregnancy we retained the conventional dose of 3 g for the trial although there is evidence to suggest that 1 g would be just as effective (Anderson *et al.* 1979; Greenwood *et al.* 1980; Greenwood & O'Grady 1977; Philipson 1983).

Every effort was made to optimize the response to single-dose treatment and the sachet of 3 g amoxycillin was therefore prescribed to be taken with food immediately before retiring in order to maximize gastrointestinal absorption and the duration of significant urinary antibiotic levels in the bladder (Greenwood & O'Grady 1977; Sutherland *et al.* 1972; Welling & Tse 1982). It was also hoped that this would reduce the incidence of side-effects. The high success rate achieved for single-dose therapy would suggest that this is a very effective method of administering single-dose treatment, although the advantage of being able to ensure patient compliance was lost. However, with one exception, neither treatment group in this study reported significant side-effects. It is unusual for amoxycillin and ampicillin not to be associated with a small though definite number of side-effects and our failure to elicit such symptoms may be due to the 6-week delay after treatment before the patient was questioned. There is, though, no evidence to support the claim that 3 g of amoxycillin is associated with a high incidence of drug-induced side-effects (Leigh *et al.* 1980).

Souney & Polk (1982) reviewed single-dose therapy for urinary tract infection in women and pointed out the great variation in protocols adopted; they recommended that efforts should be taken to introduce standardization. We would agree with this and we have therefore adhered to a protocol which utilized the definitions of the MRC Bacteriuria Committee. Implementation of these definitions led to this trial using a single freshly voided MSU for diagnosis of bacteriuria. Previous workers have used either an MSU sample followed by suprapubic aspirate (Campbell-Brown & McFadyen 1983) or catheter specimen (Harris *et al.* 1982), or two mid-stream specimens whether consecutive (Brumfitt *et al.* 1970) or not (Reeves 1975), or a single MSU (Ronald *et al.* 1976; Williams & Smith 1970). It is recognized that a single MSU specimen, when positive, has only an 80% accuracy for the diagnosis of bacteriuria (Association of Clinical Pathologists 1973). This has obvious implications when considering treatment results (*vide infra*), but we felt justified in using this index since all previous workers have used single MSU specimens when assessing treatment response and it is the commonly used criterion in clinical practice (Brumfitt *et al.* 1983). Furthermore, inclusion of a conventional treatment control group prevents any bias in favour solely of the single-dose treatment group.

The published reports on single-dose treatment in pregnant women have studied only asymptomatic antenatal bacteriuria. As the intention of this trial was to assess single-dose management of bacteriuria in the obstetric population, we have followed the example of Brumfitt *et al.* (1982) and included symptomatic patients where there was no clinical evidence of upper urinary tract involvement. Patients in the latter category were excluded since it is recognized that single-dose treatment is inferior to conventional regimens when there is a renal involvement (Ronald *et al.* 1976). Although our work detected no difference in treatment response between symptomatic and asymptomatic patients the numbers managed by single-dose therapy in each group were insufficient to allow definite conclusions to be drawn about the comparative efficacy of this approach in the two types of case.

Bacteriuria in the puerperium is recognized to be an extension of the antenatal state which can persist for several weeks (Muellner 1939). Post-partum bacteriuric patients were included in this trial as it is our department's policy to treat them. Interpretation of urine specimens is complicated in postnatal women by the increased risk of contamination and this was confirmed by our findings. But on physiological grounds puerperal patients would be expected to give similar results to antenatal patients and the rates of bacteriuria and response to treatment were indeed found to be the same in both groups.

The pattern of organisms isolated and the incidence of ampicillin resistance is similar to that reported in other studies (Brumfitt *et al.* 1970, 1982; Campbell-Brown & McFadyen 1983; Harbord & Grüneberg 1981). The results would suggest that nitrofurantoin and nalidixic acid may be more appropriate agents than amoxycillin for a study into single-dose treatment in obstetric patients since a greater proportion of pathogens was sensitive to these drugs. Although the numbers involved are small we found a highly significant difference between the stage at which treatment failure was detected in the two groups. This emphasizes the importance of an adequate follow-up period.

Our cure rates for both treatment groups are remarkably high when compared with previously published results (Table 1) where other workers have either assessed single-dose treatment to be ineffective or have achieved success rates in the expected range of 65–75% (Brumfitt *et al.* 1982). Our results are comparable with success rates recorded for single-dose amoxycillin treatment in non-pregnant women (Souney & Polk 1982) and are only matched in the obstetric field by Ronald *et al.* (1976) where infection was localized by an antibody coating technique to the lower urinary tract and by Campbell-Brown & McFadyen (1983) in a small population of Indian patients. One possible explanation for our exceptional results could be that they are artificially high due to false-positive diagnosis arising from the criteria used to assess bacteriuria. Even allowing for the inherent inaccuracy in this method of diagnosing urinary tract infection, our results remain impressive and we therefore believe our findings to be a true reflection of the response of our particular obstetric population to the treatment regimens used.

Since our study was constrained by the trial period, failure to demonstrate a statistically significant difference may be related to the sample size as revealed by the β error associated with the test statistic (Altman 1983). Balancing this limitation on our conclusion that no significant difference exists between the efficiency of the two treatment regimens in the management of bacteriuria in obstetric patients is the fact that the test statistic P value is unequivocal.

Therefore, in our opinion, a single dose of 3 g amoxycillin is safe, effective and not significantly different from conventional 7-day ampicillin treatment of bacteriuria in pregnancy and the puerperium. In view of the potential advantages of this form of treatment in terms of patient compliance, drug cost and minimization of side-effects we would recommend that a single dose of 3 g of amoxycillin be considered for the management of uncomplicated bacteriuria in pregnancy.

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Microaerophilic/anaerobic bacteria as a cause of urinary tract infection in pregnancy

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Summary. The involvement of microaerophilic/anaerobic bacteria as a cause of urinary tract infection was investigated by appropriate culture of urine samples obtained after periurethral toilet from 48 pregnant women admitted to hospital with urinary tract symptoms. Significant bacterial counts were demonstrated in 28 of these patients; 24 were due to microaerophilic/anaerobic organisms, and the remaining four were due to established urinary pathogens. In 25 pregnant women admitted without urinary tract symptoms, who were used as controls, four had significant bacterial counts, all of which were due to microaerophilic/anaerobic organisms. It is concluded that these organisms may be responsible for urinary tract symptoms in pregnant women when no significant growth is demonstrated on urinary culture by conventional methods.

The failure to demonstrate significant bacteriuria in patients with symptomatic urinary tract infection has been variously attributed to the presence of antibacterial substances in the urine, conventional pathogens in lower numbers than are normally considered significant (Stamm *et al.* 1980, 1982), infection with *Chlamydia trachomatis*, or to infection with microaerophilic or obligatory anaerobic bacteria which may not be cultured or may be disregarded.

Reports of a link between obligatory anaerobic bacteria and symptomatic urinary tract infection have been relatively rare and most are associated with abnormalities of the tract (Swami *et al.* 1980). Attempts have been made to incriminate microaerophilic and anaerobic lactobacilli (Maskell *et al.* 1979; Drabu & Sanderson 1980) as urinary pathogens, especially in the dysuria and frequency syndrome (urethral syndrome) in women but other investigators have discredited the regular involvement of these organisms (Brumfitt *et al.* 1981). The unequivocal involvement of microaerophilic bacteria has, however, in some cases, been well documented (Brumfitt *et al.* 1980).

This study was undertaken to establish the incidence of microaerophilic bacteriuria in pregnant women with and without urinary symptoms.

Subjects and methods

Subjects

Two groups of patients were examined. The first consisted of pregnant women admitted to the Royal Maternity Hospital, Belfast with symptoms of urinary tract infection, defined as dysuria and frequency with or without loin pain. There were 48 consecutive patients in this group.

The second group included 25 women admitted to the above hospital during the same period, but for reasons other than urinary tract infection.

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Urine collection

An initial pair of specimens was collected on admission—an early stream specimen (ESSU) and a midstream specimen (MSSU)—without preparative toilet. Subsequently a second pair of ESSU and MSSU was collected after thorough anterior–posterior cleaning of the periurethral region with sponges soaked in green soap. Using this cleansing procedure a third pair of specimens was collected within the first 24 h of admission and a fourth pair after 48 h. A fifth pair was collected when possible 5–7 days after admission. The procedure was carried out with the assistance of the midwifery staff.

Urine examination

Urine was examined microscopically for bacterial cells and for white and red blood cells. Bacterial counts were made within 3 h of urine collection. Urine, undiluted and in 10-fold dilution, was plated using a standard urine loop delivering 1 μl onto several media incubated under appropriate conditions. The following media and incubation conditions were used. (1) Cystine–lactose–electrolyte deficient agar (CLED, Oxoid) incubated aerobically. (2) MRS Ragosa agar (MRS, Oxoid) incubated in 10% CO_2. (3) Trypticase soy agar (TSA, Oxoid) containing 5% lysed blood, 5 μg/ml haemin, 0·5 μg/ml menadione and 100 μg/ml neomycin incubated under conventional anaerobic conditions using Oxoid gas generators in Oxoid anaerobic jars. (4) Another TSA plate without neomycin. (5) Chocolate agar incubated in 10% CO_2. All plates were incubated at 37°C and were examined daily for 4 days.

Bacterial identification

Catalase-negative Gram-positive isolates growing on MRS agar and showing a green discoloration on chocolate agar were designated *Lactobacillus* spp. Isolates of lactobacilli were further differentiated by virtue of their sugar fermentation patterns. For this purpose the sugar substrates found to give most discrimination among isolates were arabinose, galactose, lactose, maltose, mannitol, melezitose, melibiose, raffinose, salicin, sorbitol, trehalose and aesculin hydrolysis. *Corynebacterium* spp. were identified solely on the basis of their catalase reaction and Gram reaction.

Gram-negative aerobic and facultatively anaerobic bacilli, and catalase-negative and catalase-positive Gram-positive cocci accepted as established urinary pathogens were identified by normal methods after culture on CLED agar and chocolate agar.

Significant bacteriuria

A significant bacteriuria was defined as the presence of 10^5 colony-forming units per millilitre of urine (cfu/ml).

Antibiotic sensitivity tests

Tests were carried out by the methods of Stokes & Waterworth (1972) using DST sensitivity test agar (Oxoid) with 5% lysed blood added. Sensitivity was determined to ampicillin (disc strength 25 μg), cephradine (30 μg), nitrofurantoin (200 μg), nalidixic acid (30 μg), sulphamethoxazole (25 μg), trimethoprim (1·25 μg), mecillinam (25 μg), mezlocillin (75 μg) and gentamicin (10 μg)

Results

A significant bacteriuria of 10^5 cfu/ml was detected in 28 patients in specimens collected after periurethral cleansing in the 48 women with urinary tract symptoms included in the study. Among the 25 control patients without urinary symptoms a significant bacteriuria was detected in only four patients. The incidence of bacteriuria and of specifically microaerophilic/anaerobic bacteriuria (Table 1) in the study populations was significantly different ($P < 0·01$).

In all the symptomatic bacteriuric patients, excepting two, similar significant numbers of

Table 1. Incidence of bacteriuria and microaerophilic/anaerobic bacteriuria in pregnant women admitted with and without urinary tract symptoms

	With symptoms ($n=48$)	Without symptoms ($n=25$)
With any bacteriuria	28	4
With only microaerophilic/ anaerobic bacteriuria	24	4
Without bacteriuria	20	21

organisms were found in the first unprepared specimens and in subsequent specimens collected after periurethral toilet. In one patient significant numbers were only encountered in specimens collected after periurethral toilet, and in another patient significant counts were regularly recovered only from early stream specimens of urine and not from midstream specimens. Of the abacteriuric symptomatic patients, nine showed significant counts only before periurethral toilet, six yielded mixed growth throughout the sampling period and five yielded no significant counts.

Four asymptomatic control patients yielded significant counts before and after periurethral toilet, all of which were anaerobic lactobacilli. In the remaining 21 asymptomatic control patients, nine yielded significant counts, but only before the appropriate periurethral toilet had been carried out; three yielded mixed growths throughout the sampling period and in a further nine patients, specimens yielded no significant counts at any time.

The organisms isolated from the symptomatic and asymptomatic patients included *Lactobacillus* spp. (25), *Corynebacterium* spp. (1), anaerobic Gram-positive cocci (2). Four symptomatic women showed infection with established pathogens which were *Proteus mirabilis* (1) and *Staphylococcus* spp. (3).

Among the 28 symptomatic bacteriuric patients counts of $>10^7$ cfu/ml of urine were common. The counts obtained in the 21 symptomatic lactobacilluric and four asymptomatic lactobacilluric patients were high; all but three gave counts of $>10^6$ cfu/ml and 13 yielded counts of $>10^7$ cfu/ml. Three symptomatic patients yielded counts between 10^5 and 10^5 cfu/ml. No symptomatic patient yielded counts of $<10^5$ cfu/ml.

In some patients with symptomatic urinary tract infection and lactobacilluria, cultures of lactobacilli isolated at different sampling times were collected and stored for comparison. Comparisons were based on acid production from a range of carbohydrate substrates, aesculin hydrolysis, nitrate reduction and arginine hydrolysis. Lactobacillus isolates from 12 symptomatic patients with persistent lactobacilluria were examined in detail. In 10 of 12 patients all lactobacillus isolates from the same patient, varying in number between four and eight, gave the same biochemical test reactions. In two patients some variations in biochemical test results were recorded.

Twelve lactobacillus isolates from symptomatic patients were identified according to the methods described by Cowan & Steel (1974) as *L. acidophilus* (5), *L. jenseni* (5) *L. leishmanni* (1) and *L. casei* (1).

The majority of lactobacillus isolates were sensitive to ampicillin, mecillinam and mezlocillin. Variable sensitivity to nitrofurantoin and cephradine was recorded, but both trimethoprim and sulphamethoxazole were inactive.

Incubation in an atmosphere enriched with 10% CO_2 was the most useful environmental factor used to hasten growth of these organisms, and the majority of isolates were detected on MRS agar or chocolate agar under these conditions. Nevertheless culture of lactobacilli from urine specimens could require up to 72 h incubation before a definitive result could be issued. Furthermore antibiotic sensitivity could only be made available approximately 96 h after receipt of the specimen. A few isolates were detected under anaerobic conditions before their appearance in CO_2-enriched atmosphere on MRS or chocolate agar.

Discussion

The cornerstone of this study undertaken in pregnant patients was the collection of urine specimens after careful periurethral toilet. When these precautions are taken there is a statistically significant difference ($P<0{\cdot}01$) between the incidence of bacteriuria in the study populations. Significant bacterial counts were found in 28 of 48 pregnant symptomatic patients; 24 of these 28 significant growths were microaerophilic/anaerobic bacteria, mainly lactobacilli. The vast majority were found in numbers greater than 10^6 cfu/ml urine and counts of 10^8 cfu/ml were encountered. The low incidence of established urinary pathogens in this pregnant symptomatic group was remarkable.

In at least some patients the same microaerophilic/anaerobic bacteria were found in repeat specimens, as judged by their biochemical reactions. The majority were lactobacilli and represented species usually considered to be vaginal commensal bacteria. Their sensitivity to antibiotics compared closely with that reported by other workers (Maskell *et al.* 1979; Brumfitt *et al.* 1981).

In one patient the early stream specimens of urine regularly showed high counts (10^7 cfu/ml) while yielding only low counts (10^4 cfu/ml) in the midstream specimens. This is very weak contributory evidence in support of the thesis that these microaerophilic/anaerobic bacteria are often localized in the periurethral or urethral area.

The results confirm the findings of Maskell *et al.* (1979) that microaerophilic bacteria may be cultured from patients with urinary symptoms whose urine does not yield recognized pathogens. It would have been desirable that treatment with an antibiotic active against those bacteria could alleviate symptoms with an accompanying removal of the bacteriuria. This information could not easily be collected from a symptomatic group usually enjoying only a brief stay in hospital. The merits or necessity of treatment of urinary symptoms in such patients is in any case a continuing matter of debate in the non-pregnant population; certainly it would be impossible and undesirable to remove the periurethral and vaginal reservoir of these organisms. Although Maskell *et al.* (1983) have noted rapid symptomatic relief in some antibiotic-treated patients with urethral syndrome, it was also noted that symptoms and organisms tended to reappear. Nevertheless, the well-established link between asymptomatic bacteriuria and acute pyelonephritis in pregnancy and the association between the latter and preterm labour justifies an aggressive therapeutic approach. When symptoms warrant treatment the choice and immediate use of an antibiotic such as ampicillin seems appropriate since in this study the majority of cultures were sensitive to it.

The association of microaerophilic bacteria and symptomatic urinary infection in patients with 'urethral syndrome' has received considerable recent attention but remains largely unresolved. The evidence suggests that if these organisms are primary pathogens the urethral syndrome associated with them has a long natural history (Maskell *et al.* 1983). This may not be the case with the pregnant women considered here where symptoms may be related to local paraurethral or urethral changes occurring during pregnancy. Certainly we have no evidence to suggest that these symptomatic patients with microaerophilic bacteriuria had established histories of recurrent urinary symptoms with or without detected bacteriuria.

The work confirms the findings of Maskell *et al.* (1979) that high numbers of microaerophilic bacteria, particularly lactobacilli, are more often found in the urine of symptomatic than asymptomatic patients.

Mycoplasma hominis (Thomsen *et al.* 1978), *Ureaplasma urealyticum* (Birch *et al.* 1981) and *Chlamydia trachomatis* (Weil *et al.* 1981) have been implicated as causes of urinary tract infection in some studies but their role is far from clear. Pregnancy may provide especially favourable conditions in some women for an upward urethral colonization by microaerophiles, especially lactobacilli. It remains unclear, however, whether the microaerophilic bacteria fill a primary pathogenic role or are secondary invaders advancing in response to other infective or non-infective changes in the lower urinary tract.

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Increased sensitivity to thromboplastin synthesis in blood monocytes from pre-eclamptic patients

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Summary. The thromboplastin activity in blood monocytes was investigated in third-trimester pregnancies comprising 11 patients with severe pre-eclampsia, 10 with essential hypertension and 18 normal pregnancies. Thromboplastin activity in unstimulated monocytes from the severe pre-eclamptic group was on average three times that found in the normal pregnant group, but variation was wide and the differences were not statistically significant. Thromboplastin activity in endotoxin-stimulated monocytes was significantly higher in the severe pre-eclamptic group than in the other two groups (normal and chronic hypertensive). In the severe pre-eclamptic group, there was a significant negative linear correlation between thromboplastin activity of the endotoxin-stimulated monocytes and factor VII. Fibrinogen, factor VII and α_2-antiplasmin were significantly lower in the severe pre-eclamptic group than in the normal pregnant group, whereas no differences were observed in factors V, VIII, AT-III and prekallikrein.

The aetiology of pre-eclampsia is unknown, but there is now considerable evidence to suggest that intravascular coagulation may play a part in its pathogenesis (Howie 1977). Such a concept is attractive because a process of intravascular coagulation could explain many of the clinical features of pre-eclampsia by obstructing blood flow to the placenta, kidney, liver and brain. But there is still considerable controversy as to whether it is a primary factor in the aetiology of the condition, or secondary to other changes, possibly immunological, and whether the intravascular coagulation is disseminated or localized to certain organs (MacGillivray 1983). Evidence in favour of local coagulation and fibrin deposition is based on the examination of renal biopsy specimens (Pollak & Nettles 1960) and placental bed biopsy specimens (Brosens 1977).

The cause of activation of the coagulation system in pre-eclampsia is not clear, but release of thromboplastin into the maternal circulation may be relevant. Thromboplastin (factor III), a protein–phospholipid complex, is the most powerful trigger of blood coagulation known. It has been proposed that trophoblastic fragments from the damaged placenta enter the circulation in pre-eclampsia and act as the stimulus to intravascular coagulation (Page 1972). Dalaker *et al.* (1983) have shown that mouse placental cells naturally synthesize thromboplastin; and it is also established that human monocytes possess thromboplastin activity and that stimulated monocytes generate a substantial amount of thromboplastin (Østerud & Bjørklid 1982*a*). Recently (Øian *et al.* 1985) we have found that the thromboplastin activity in both unstimulated and endotoxin-stimulated monocytes isolated from peripheral blood in normal pregnant women was only 40% of the activity found in healthy non-pregnant women. In this report we have examined the thromboplastin activity of

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Correspondence: Pål Øian, Department of Obstetrics and Gynaecology, University of Tromsø, 9012 Tromsø, Norway blood monocytes as well as some of the clotting factors in pregnant chronic hypertensive and pre-eclamptic patients. The aim of the study was to see if the low-grade intravascular coagulation seen in many of these patients is induced by activation of the monocytes.

Subjects and methods

Patients

Three groups of pregnant women were studied.

Severe pre-eclamptic. The 11 patients in this group had a blood pressure of ≥160/100 mmHg and proteinuria in excess of 3·0 g/l in a 24-h urine specimen. Nine of the patients were nulliparae; none had a history of hypertension or chronic renal disease, and all became normotensive 6 weeks postpartum. Four of the patients were delivered by caesarean section. Six of the patients received methyldopa and two hydralazine at the time of the investigation.

Chronic hypertensive. The 10 patients included in this group had essential hypertension before pregnancy; four were nulliparae. One patient was delivered by caesarean section, two patients received a beta blocker and another two methyldopa.

Normal pregnant. The third group included 18 normotensive women in the third trimester, none of whom had a history of hypertension or other disease. Their pregnancies were uneventful and all had normal vaginal deliveries. None of the normal pregnant women was taking any kind of medical treatment.

Further characteristics of the patients studied, together with the birthweights of their infants are given in Table 1.

Methods

Blood collection. Blood was obtained from all the patients in late pregnancy (but at least 24h before delivery) and on the third day postpartum. Blood was drawn into containers (Vacutainer) containing either 0·10 M sodium citrate or heparin (15 U/ml final concentration). Plasma of citrated blood was obtained by centrifugation at 12 000 *g* for 10 min. The plasma samples were then stored at −70°C until all plasma samples were analysed on the same day for the different coagulation activities. Blood used for monocyte isolation or incubation with endotoxin was kept at room temperature and always subjected to further treatment within 30 min.

Isolation of mononuclear cells. A 1-ml portion of blood was diluted with an equal volume of 0·15 M NaCl and subjected to centrifugation on Lymphopaque (Nyegaard A/S, Oslo, Norway) as described by Bøyum (1976). The band with mononuclear cells was pipetted off, washed with

Table 1. Some characteristics of the three groups studied and the birthweights of the infants

	Normal pregnant (n=18)	Chronic hypertensive (n=10)	Severe pre-eclamptic (n=11)
Age (years)	23·9 (3·4)	32·1 (6·1)****	26·2 (5·6)
Gestational age (weeks)			
at blood sampling	34·5 (3·6)	37·2 (4·5)	33·4 (4·5)
at delivery	39·6 (1·7)	37·9 (4·3)	33·8 (4·1)
(range)	(36–42)	(29–40)	(29–41)
Blood pressure at blood sampling (mmHg)			
Systolic	118 (7)	159 (12)****	185 (11)****
Diastolic	77 (6)	103 (6)****	117 (10)****
Proteinuria at blood sampling (g/24 h)	0	0·7 (0·9)****	7·6 (6·5)****
Birthweight (g)	3546 (422)	2984 (1025)	1756 (916)****

Results are mean (SD).
Chronic hypertensive or severe pre-eclamptic *vs* normal pregnant.
* P (P') <0·05; **** P (P') <0·001.

10 ml 0·15 M NaCl, and the cells collected by centrifugation at 1200 *g* for 10 min. The cells were resuspended and counted, and the total number of monocytes differentiated as described by Yam *et al.* (1971). The cell suspensions were frozen at −70°C until tested for thromboplastin activity.

Measurement of thromboplastin activity. An assay based on the ability of thromboplastin to accelerate the activation of factor X by factor VII was used (Østerud & Bjørklid 1982*a*; Østerud *et al.* 1981). To calibrate the assay, different dilutions of crude human brain thromboplastin, prepared by us, were tested in the same system (Østerud & Bjørklid 1982*a*). The thromboplastin activity in 10^6 lysed monocytes was then expressed as a percentage of the known standard preparation. The mononuclear cells isolated contained considerable numbers of lymphocytes, but contamination of lymphocytes in the monocyte preparation has no effect in our system for measuring thromboplastin activity (Østerud & Bjørklid 1982*a*).

Endotoxin stimulation of blood monocytes. Freshly drawn heparinized blood (1 ml) in 1·3 cm × 8·0 cm polycarbonate tubes was incubated with *Escherichia coli* 026:B6 endotoxin (Difco Laboratories, Detroit, MI) for 2 h at 37°C. The mononuclear cells were then immediately isolated, lysed by freezing and thawing, and thromboplastin activity measured.

Clotting assays. Factors V, VII and VIII were measured in one stage clotting assays (Østerud & Rapaport 1970). AT-III, prekallikrein and α_2-antiplasmin were analysed by utilizing kits from KABI, Sweden, according to the manufacturer. Fibrinogen was quantitated according to the method described by Inada *et al* (1978).

Statistics. The data are presented as means and standard deviations. Statistical significance was determined using the pooled *t*-test (P) and the Mann–Whitney test (P'), and a P (P') value <0·05 was considered statistically significant. Correlation coefficients were calculated by the least-squares method.

Results

The thromboplastin activity in blood monocytes and the clotting factors are presented in Table 2. The results on the third day postpartum are given in Table 3. The thromboplastin activity in the normal pregnant and severe pre-eclamptic group are also presented in Fig. 1 and the clotting factors in Fig. 2.

Thromboplastin activity of blood monocytes

The thromboplastin activity of the isolated monocytes in the severe pre-eclamptic group (mean 0·15, SD 0·28 × 10^{-3}%/10^6 cells) was on average three times that of the normal pregnant group (mean 0·05, SD 0·04 × 10^{-3}%/10^6 cells),

Table 2. The thromboplastin activity of blood monocytes and clotting factors in normal pregnant, chronic hypertensive and severe pre-eclamptic patients

	Normal pregnant (n=18)	Chronic hypertensive (n=10)	Severe pre-eclamptic (n=11)
Thromboplastin activity (10^{-3}%/10^6 cells)			
Unstimulated	0·05 (0·04)	0·07 (0·09)	0·15 (0·28)
Endotoxin stimulated	3·21 (2·82)	2·51 (1·74)	5·72 (3·33)*
Factor V (%)	103 (24)	98 (12)	88 (14)
Factor VII (%)	250 (108)	157 (39)*	151 (32)**
Factor VIII (%)	143 (40)	144 (45)	125 (41)
Fibrinogen (g/l)	3·6 (0·8)	3·2 (0·5)	2·8 (0·4)**
AT-III (%)	87 (13)	106 (18)**	80 (16)
Prekallikrein (%)	99 (18)	108 (27)	96 (16)
α_2-antiplasmin (%)	85 (15)	89 (8)	65 (28)*

Results are means (SD).
Chronic hypertensive or severe pre-eclamptic *vs* normal pregnant.
* P (P') <0·05; ** P (P') <0·01.

Table 3. The thromboplastin activity of blood monocytes and clotting factors post partum in normal pregnant, chronic hypertensive and severe pre-eclamptic patients

	Normal pregnant (n=18)	Chronic hypertensive (n=10)	Severe pre-eclamptic (n=11)
Thromboplastin activity (10^{-3}%/10^6 cells)			
Unstimulated	0·05 (0·05)	0·05 (0·04)	0·26 (0·58)
Endotoxin stimulated	2·88 (2·20)	2·64 (1·78)	4·70 (4·59)
Factor V (%)	101 (29)	157 (39)****	118 (17)
Factor VII (%)	158 (25)	143 (25)	137 (35)
Factor VIII (%)	153 (63)	121 (58)	166 (34)
Fibrinogen (g/l)	2·7 (0·7)	3·9 (0·7)***	3·9 (0·8)****
AT-III (%)	89 (24)	111 (22)*	121 (12)***
Prekallikrein (%)	77 (15)	92 (27)	86 (23)
α_2-antiplasmin (%)	89 (26)	79 (23)	91 (26)

Results are means (SD).
Chronic hypertensive or severe pre-eclamptic *vs* normal pregnant.
* P (P') <0·05; *** P (P') <0·005; **** P (P') <0·001.

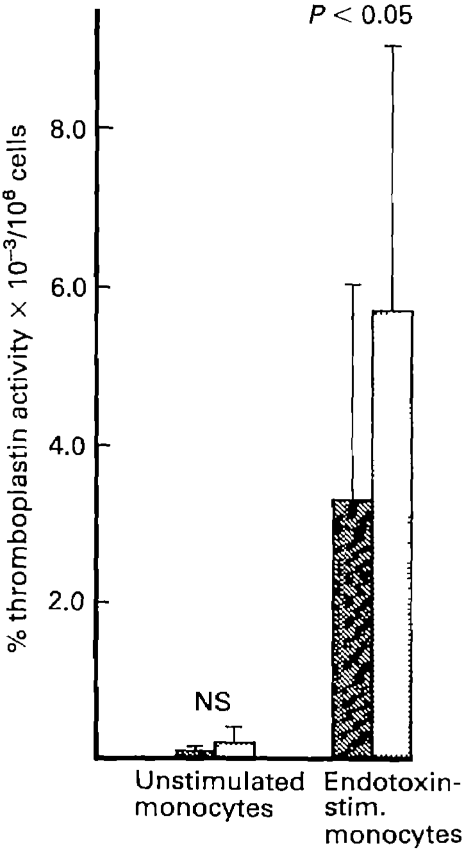

Fig. 1. Thromboplastin activity of unstimulated and endotoxin-stimulated blood monocytes in the normal pregnant group (▨ n=18) and the severe pre-eclamptic group (☐ n=11)

but variation was wide and the differences were not statistically significant. There was no difference between the chronic hypertensive and normal pregnant group (Table 2). In both groups there was no significant difference between the thromboplastin activity before delivery and on the third day postpartum (Table 3).

The sensitivity of blood monocytes to endotoxin stimuli

The thromboplastin activity of endotoxin-stimulated monocytes was significantly higher (P<0·05, P'<0·02) in the severe pre-eclamptic group (mean 5·72, SD 3·33 × 10^{-3}%/10^6 cells) than in the normal group (mean 3·21, SD 2·82 × 10^{-3}%/10^6 cells). In the chronic hypertensive group the thromboplastin activity was lower (mean 2·51, SD 1·74 × 10^{-3}%/10^6 cells) than in the normal pregnant group. Thus, the thromboplastin activity in the pre-eclamptic group was more than double that in the chronic hypertensive group (P<0·02, P'<0·01). There was no significant difference in the response before delivery and on the third day postpartum.

Correlation between thromboplastin activity and factor VII

In the severe pre-eclamptic group, there was a significant negative linear correlation between the thromboplastin activity of endotoxin-stimu-

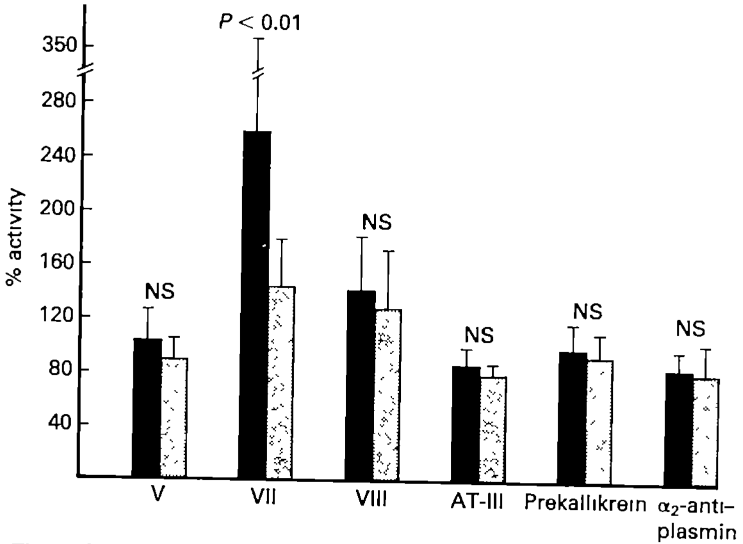

Fig. 2. Clotting factors in the normal pregnant group (■ n=18) and the severe pre-eclamptic group (▨ n=11).

lated monocytes and factor VII (r = $-0{\cdot}64$, $P<0{\cdot}05$). In the chronic hypertensive and the normal pregnant group there was no such relation.

Clotting factors

In the severe pre-eclamptic group, factor VII activity (mean 151, SD 32%) was on average only 60% of the activity in the normal pregnant group (mean 250, SD 108%) ($P<0{\cdot}01$, $P'<0{\cdot}001$). A significant reduction in fibrinogen concentration ($P<0{\cdot}01$, $P'0{\cdot}001$) and in α_2-antiplasmin ($P<0{\cdot}05$, $P'<0{\cdot}05$) was also observed in the severe pre-eclamptic compared with the normal group (Table 2). No change was observed in factors V, VIII, AT-III and prekallikrein.

In the chronic hypertensive group, factor VII was significantly lower ($P<0{\cdot}02$, $P'<0{\cdot}01$) than in the normal pregnant group, whereas AT-III was significantly higher ($P<0{\cdot}01$, $P'<0{\cdot}01$). In the other clotting factors tested, no change was observed.

On the third day postpartum, fibrinogen concentrations were significantly higher both in the pre-eclamptic ($P<0{\cdot}001$, $P'<0{\cdot}001$) and chronic hypertensive groups ($P<0{\cdot}001$, $P'<0{\cdot}003$) than in the normal group. This is because in the normal group fibrinogen concentration was significantly lower ($P<0{\cdot}005$, $P'<0{\cdot}005$) at 3 days postpartum than in late pregnancy, whereas in the pre-eclamptic and chronic hypertensive groups fibrinogen concentrations were higher in the postpartum period than in late pregnancy.

The AT-III activity was significantly higher on the third day postpartum both in the severe pre-eclamptic ($P<0{\cdot}005$, $P'<0{\cdot}001$) and chronic hypertensive groups ($P<0{\cdot}05$, $P'<0{\cdot}03$) than in the normal group (Table 3). In the chronic hypertensive group, factor V was increased ($P<0{\cdot}001$, $P'<0{\cdot}001$) postpartum.

Discussion

In the present study we have shown that severe pre-eclampsia may be associated with elevated levels of thromboplastin activity in the circulating monocytes. In unstimulated monocytes thromboplastin activity was on average three times higher in pre-eclampsia than in normal pregnancy, although not statistically significant. In the endotoxin-stimulated monocytes thromboplastin activity was significantly higher in the severe pre-eclamptic group than in the normal pregnant group. Only three of the infants in the pre-eclamptic group were below the 10th centile of weight for gestation. Thromboplastin activity in monocytes in these women was not statistically significantly different from that in the other pre-eclamptic patients.

Human monocytes can be stimulated in various ways, e.g. by endotoxin (Rivers *et al.* 1975), complement factors (Prydz *et al.* 1977) and immune complexes (Rothberger *et al.* 1977;

Prydz *et al.* 1979). The mechanisms explaining the increased thromboplastin activity in monocytes and the increased sensitivity to stimuli in the pre-eclamptic patients are unknown. One possibility is that immune complexes formed by maternal antibody and trophoblast antigen might activate complement. It is known that thromboplastin synthesis in monocytes is totally dependent on the presence of complement (Østerud & Eskeland 1982) so that the rise in thromboplastin activity might be due to complement activation which occurs in pre-eclampsia (Johansen *et al.* 1981). Another explanation could be that in pre-eclampsia monocytes disappear from the circulation due to vascular injury, and that a new generation of monocytes, more sensitive to stimuli for thromboplastin synthesis, take their place.

The low factor VII concentration in the pre-eclamptic patients may be caused by the binding of factor VII to thromboplastin exposed on the surface of the monocytes. Recent reports (Østerud & Bjørklid 1982*b*; Østerud 1983) suggest that stimulated monocytes bind factor VII in the presence of calcium ions and that this binding of factor VII is directly related to the exposure of thromboplastin on the surface of the stimulated monocytes. Factor VII is converted to an active form VIIa by factor Xa in the presence of phospholipids, or by factor IXa and factor XIIa. Factor VIIa is probably the form of factor VII bound to the monocytes (Østerud & Bjørklid 1982*b*). But the chronic hypertensive group also showed a low factor VII level and their thromboplastin activities were normal, so that the low factor VII levels found in this study may have other explanations.

Increased fibrinogen concentration during normal pregnancy is well known, and our finding of reduced concentration postpartum may be explained by reduced production, and/or increased consumption, following placental separation (Bonnar 1973). The increments in fibrinogen concentration postpartum in the severe pre-eclamptic and chronic hypertensive groups could be explained by fibrinogen behaving like an acute-phase reactant.

The decrease in α_2-antiplasmin concentration during pregnancy in the severe pre-eclamptic group probably reflects consumption due to increased fibrinolysis.

Weenink *et al.* (1983) found that AT-III concentration decreased in severe pre-eclampsia, and they provided evidence that AT-III depression in pre-eclampsia is caused by increased consumption rather than decreased synthesis or urinary loss. Also in our study a tendency for decreased AT-III level was observed in the severe pre-eclamptic group, although this was not statistically significant possibly because of our small sample size. Our finding of increased AT-III levels on the third day post-partum both in the severe pre-eclamptic and chronic hypertensive group, may be explained by reduced consumption after delivery.

In conclusion, the increased thromboplastin activity of blood monocytes in pre-eclamptic patients may possibly play a part in the induction of intravascular coagulation seen in this disease. The sensitivity of blood monocytes to thromboplastin synthesis is known to vary widely between individuals (Østerud & Bjørklid 1982*a*) and this may explain the inconstant finding of coagulation disturbances seen in pre-eclamptic patients.

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A comparison of prostaglandin E_2 pessaries and laminaria tents for ripening the cervix before termination of pregnancy

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Summary. Forty primigravid women aged 15–45 years were randomly allocated to receive either an intravaginal pessary of 3 mg prostaglandin E_2 (PGE_2) or an intracervical 5-mm laminaria tent (LT) 12–16 h before termination of pregnancy at 6–14 weeks gestation. The degree of dilatation of the cervix at operation and its resistance to further dilatation during the procedure were assessed by a 'blind' operator. Laminaria tents were more effective in achieving dilatation and softening of the cervix than were PGE_2 pessaries and in 40% of women no further dilatation was necessary. There were no associated side-effects or complications. A cervical tear occurred in two of 20 patients treated with PGE_2 pessaries and all 20 required further dilatation of the cervix. Laminaria tents provide a simple, safe, acceptable and effective means of 'ripening' the cervix prior to termination of early pregnancy.

Cervical trauma and uterine perforation are well recognized complications of termination of pregnancy effected by cervical dilatation and uterine curettage (Grimes & Cates 1979) particularly in primigravid women (Harlap *et al.* 1979). The incidence of subsequent cervical incompetence is increased by a factor which has been put as high as 10 times that of controls (Wright *et al.* 1972) although this is almost certainly pessimistic (Harlap *et al.* 1979).

Various methods of 'ripening' the cervix, by inducing gradual softening and dilatation have been employed in an attempt to reduce these risks. Hydrophilic organic substances, inserted into the cervical canal, have been used as abortifacients for more than a century, the best known being the seaweed *Laminaria digitata* or *L. japonicum*. These substances absorb fluid and expand over several hours, thereby affecting gradual cervical dilatation (Hale & Pion 1972).

Since insertion into and retention of foreign bodies within the cervical canal carries a potential risk of ascending infection this practice has not gained general acceptance, but the short time of insertion makes this hazard minimal. Furthermore laminaria have been extensively used in the pre-operative preparation of the cervix to facilitate its dilation (Golditch & Glasser 1973).

More recently prostaglandins (PG) or their analogues have been successfully employed in inducing dilatation and softening of the cervix prior to induction of labour or termination of pregnancy. However, in effective doses, whether administered orally (Heinzl & Andor 1981), intramuscularly (Christensen *et al* 1983), intravaginally (Lauersen *et al.* 1982) or intracervically (Rath *et al.* 1983), systemic upsets, such as vomiting and diarrhoea are frequent side-effects. Additionally, by inducing uterine contractions, these compounds may cause pain and bleeding.

This study was undertaken to compare the relative efficacy and side-effects of the intracervical insertion of laminaria tents and intravaginal administration of PGE_2 in a dose below that at which systemic side-effects occur (Mackenzie & Fry 1981), in order to establish a safe, effective and acceptable means of 'ripening' the cervix prior to termination of first-trimester pregnancy.

Materials and methods

Batches of pessaries containing 3 mg of an alcoholic solution of PGE_2 in a non-polar base, Witepsol H15, were prepared by the hospital pharmacy. Quality control using high-performance lipid chromatography to assay prostaglandin content confirmed that each batch contained 90–110% of the stated dose of active compound. Pessaries were stored at −4°C and used within 3 weeks of preparation.

Laminaria tents, 5 mm in diameter, were purchased in packs sterilized by gamma irradiation, from Eschman Brothers and Walsh Limited, Sussex.

Forty primigravid women who had been accepted for vaginal termination of first-trimester pregnancy were recruited into the study after obtaining their written and informed consent All patients were admitted to hospital the day before operation and were randomly allocated to treatment with either a PG pessary or a laminaria tent which was inserted the same evening. Where any doubt existed as to exact gestational age after history and examination, this was determined by ultrasound scan.

Vaginal pessaries were placed high in the posterior fornix and the laminaria tents were inserted into the cervical canal under direct vision, using an aseptic technique and without the use of cervical grasping forceps. The same investigator (S.K.) inserted all pessaries and laminaria tents. All patients were examined again 12–16 h later, prior to anaesthesia to remove the laminaria tents or to confirm that the vaginal pessaries had completely dissolved. The surgeon performing the termination thus remained 'blind' to the method of treatment used.

All terminations were performed under general anaesthesia. The cervix was dilated with graduated Hegar's dilators and suction curettage of the uterus undertaken with an appropriately sized Karmen curette. The largest dilator which would pass through the internal os without resistance was noted prior to further dilatation. The resistance of the cervix to subsequent dilatation was assessed subjectively as 'minimal', 'less than average', 'average', 'more than average' or 'severe'. Any intra-operative or postoperative complication was noted. Patients were seen 15–24 h postoperatively before discharge from hospital.

Statistical methods

Maternal age and gestation in the two groups were compared using the Mann–Whitney *U* test. Cervical dilatation prior to operation and the resistance of the cervix to further dilatation in the two groups were compared using χ^2 contingency table analysis.

Results

The results of the study are summarized in Table 1. The age and duration of pregnancy were similar in the two groups.

Insertion of the laminaria tents presented no difficulty and on no occasion was it necessary to abandon the procedure or to resort to the use of a smaller size of tent. Insertion was associated with mild cramp-like pain which persisted for several hours in nine patients. Only one patient required analgesia. Removal of laminaria tents was not associated with any difficulty or discomfort; in two patients, the tents were lying free in the vagina. None had ascended into the uterine cavity.

Table 1. Maternal age, gestation and cervical dilatation in the two groups

Treatment group	Maternal age (years) median (range)	Gestation (weeks) median (range)	Cervical dilatation (Hegar) median (range)
Laminaria tent (n = 20)	19 (15–28)	10 (8–13)	8 (3–11)
Prostaglandin pessary (n = 20)	19 (14–45)	10 (8–12)	5 (2–10)

No discomfort was reported by patients receiving prostaglandin pessaries which were more quickly and simply inserted. None of these patients experienced systemic upset following treatment.

The median dilatation of the cervix after priming and prior to operation was 8 (range 3–11) Hegar in the group receiving laminaria tents and this was significantly greater than that induced by prostaglandin E_2 (median 5, range 2–10 Hegar) ($P = 0{\cdot}001$). In eight out of 20 patients (40%), including the two in whom the tent had fallen out of the cervix, further dilatation of the cervix was not necessary, whereas this was required in all 20 women receiving intravaginal PGE_2 before suction curettage was possible.

Resistance of the cervix to further dilatation was greater in the women treated with PGE_2 than in those receiving laminaria tents ($P = 0{\cdot}023$) and in two cases a cervical tear occurred during dilatation. No cervical trauma occurred in the group who had received laminaria tents.

There were no postoperative complications in either group and, in particular, all patients remained apyrexial until discharge from hospital.

Discussion

The results of this study suggest that a 5-mm laminaria tent is more effective than a 3-mg pessary of prostaglandin E_2 in inducing dilatation and softening of the cervix in early pregnancy. Indeed, use of a laminaria tent obviated the need for further dilatation of the cervix prior to suction curettage of the uterus in a large proportion of cases. As cervical trauma results from mechanical dilatation of the cervical canal, the use of laminaria tents for pre-operative 'priming' of the cervix would appear to be superior to the use of PG pessaries in reducing complication associated with termination of pregnancy. This contention is supported by the absence of operative complications in women receiving laminaria tents, whereas a cervical tear occurred in two women treated with PG pessaries.

Dilatation of the cervix induced by laminaria tents has been attributed to their gradual expansion as they absorb water (Halé & Pion 1972), but in two cases the cervix had dilated beyond the diameter of the tent, which fell out of the cervical canal. In addition to affecting dilatation, and in common with other reports (Manabe & Manabe 1983) softening of the cervix accompanied dilatation. Increased concentrations of prostaglandin metabolites in plasma have been demonstrated after intracervical insertion of laminaria tents (Ye *et al.* 1982) and it is probable that distension of the cervix causes local release of endogenous prostaglandins which are more effective than exogenous preparations.

The reason for the poor performance of our pessaries might have been because the dose of prostaglandin was too low. A higher dose of 10 mg PGE_2 in a Witepsol base has been suggested as a more suitable dose (Mackenzie & Fry 1981) but only when the termination is to be performed as a day case procedure and an effect is therefore necessary from as early as 1 h after pessary insertion. Side-effects, including spontaneous abortion prior to operation, occur at this dose level and hence a lower dose would be more desirable when a pre-operative overnight stay in hospital is the routine. Despite the great care that was taken in the preparation, quality control and storage of PG pessaries in this trial vaginal absorption of prostaglandin is unpredictable (Khoo *et al.* 1981) and this may have been the reason for the poor response in some individuals.

The incidence of operative complications in this study was low and occurred only in the PG-treated group. The absence of postoperative pyrexia suggests that the risk of infection following insertion of laminaria tents is small, particularly when insertion is undertaken with careful regard to asepsis. However, patients were not followed up for more than 24 h and bacteriological studies were not undertaken. Work is in progress to examine these aspects further.

Mild discomfort was experienced on insertion of tents by the majority of patients although in only one was pain sufficiently severe to warrant the use of analgesia. Insertion of the PG pessaries caused no pain and side-effects were absent, but a greater and more effective dose may well have been unacceptable to many patients.

Although further comparative studies are required, pre-operative use of laminaria tents would appear to be a simple, safe, effective and acceptable means of reducing complications associated with mechanical cervical dilatation before termination of pregnancy.

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The role of cytoreductive surgery in advanced carcinoma of the ovary: an analysis of primary and second surgery

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Summary. Second operations were performed as part of planned management in 53 patients 5–7 months after starting apparently successful chemotherapy. The survival of these patients is compared with 56 other patients who did not have a second laparotomy but appeared to be responding to chemotherapy equally well. Survival advantage was seen for those who had a partial remission followed by a further debulking procedure later. However, those patients who have a clinical complete remission do not seem to benefit from a second surgical intervention.

It is now widely accepted that advanced carcinoma of the ovary is beyond surgical cure because of the widespread dissemination within the abdominopelvic cavity. However, many studies have shown an inverse relation between residual tumour size after initial operation, and response to chemotherapy and to survival (Griffiths *et al.* 1979; Smith *et al.* 1972; Tobias & Griffiths 1976; Wharton *et al.* 1975, 1979; Young *et al.* 1978). At the same time, aggressive cytoreduction by the initial surgeon is thought to exert a favourable influence on the clinical course of the disease (Griffiths *et al.* 1979; Griffiths 1975; Hudson 1968).

Another important factor in long-term survival of patients with advanced disease is the response to chemotherapy, and the induction of complete remission is essential to long-term disease-free survival (Raju *et al.* 1982; Katz *et al.* 1981; Piver *et al.* 1975; Schwartz & Smith 1980).

Recently, second operations have been incorporated into many protocols with a view to assessing response to additional therapy (chemotherapy or radiotherapy) or for further cytoreductive surgery following response to therapy. In our study of 65 patients subjected to second-look operation (SLO) for further cytoreductive surgery (Raju *et al.* 1982) we, like many other investigators, found that the patients with complete surgical response had the best prognosis (Wallach *et al.* 1975; Phillips *et al.* 1979; Kjorstad *et al.* 1977). But in our study we were disappointed to find that patients who had achieved a partial surgical response following chemotherapy in whom complete removal of residual disease was accomplished at SLO did no better than those in partial surgical remission after SLO (Raju *et al.* 1982). This study suggested that cytoreductive surgery after partially successful chemotherapy was of little value.

Thus we decided to look at those patients who had had an SLO at 5–7 months after starting chemotherapy as part of a planned treatment programme and to compare them with patients having the same chemotherapy, the same response to chemotherapy but had not been subjected to SLO. This comparison is the subject of the present study.

Patients and methods

From 1976 to 1980 a total of 155 patients with FIGO stage III and IV epithelial carcinoma of the ovary were treated, in prospective randomized studies, with either single-agent or combination chemotherapy as shown in Table 1. Forty-six patients did not respond to the additional chemotherapy and are excluded from the present study. All the patients had the initial surgery by gynaecologists outside our institute

Table 1. Chemotherapy given to 109 patients with responding tumours in relation to second-look operation (SLO)

Chemotherapy	Patients with SLO	Patients without SLO
Cisplatin 20 mg/m^2 + chlorambucil 0·15 mg/kg + adriamycin 60 mg/m^2	23	9
Cisplatin 20 mg/m^2 + chlorambucil 0·15 mg/kg	15	37
Cisplatin 100 mg/m^2	14	6
Cisplatin 20 mg/m^2 + hexamethylmelamine 300 mg	1	4
Total	53	56

and the findings at the laparotomy were forwarded to us; the histologies of the tumours of all the patients were reviewed at the Royal Marsden Hospital. Chemotherapy was commenced within 8 weeks of diagnosis and the patients were seen at 3–4 week intervals depending on the regimens used. Chemotherapy was given for 5 months and if all evidence of tumour had disappeared (clinical complete remission) or if there was <50% of all measurable tumour (clinical partial remission) patients were submitted to laparotomy. If the surgical findings suggested that no good regression had occurred, then the chemotherapy was changed to different agents. If, on the other hand, response was confirmed, then chemotherapy was continued as per protocol. In the case of patients without SLO chemotherapy was continued in all patients as per protocol. Of the 109 responding patients, 77 were in partial remission and 32 in complete remission after five to seven courses of chemotherapy on clinical and radiological assessment. Second-look operation was part of the planned therapeutic protocol for all responding cases if a total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO) and omentectomy had not been performed at initial surgery. In the event, 53 patients (group A) had a SLO. Of the 56 remaining patients (group B) no SLO was done for the following reasons: in 25 a full procedure (TAH, BSO and omentectomy) had already been performed at their first operation; in the remainder, either the patient or the referring surgeon refused further (SLO) surgery in the belief that this would not be therapeutically useful. Patients were followed up for a minimum of 7 months and a maximum of 60 months. Table 2 shows the patients' characteristics in both groups. The relation of regression of tumour, as seen at clinical, radiological and ultrasonographic examination in both group A (prior to SLO) and group B, to survival, was examined by calculating Kaplan–Meier survival curves (Peto *et al.* 1977).

Table 2 shows the extent of surgery at the initial laparotomy in the two groups of patients. Although there were more patients (45%) in group B who had TAH, BSO and omentectomy when compared with 15% in group A, the number of patients with no radiological or clinical evidence of disease before the commencement of chemotherapy in both groups were 13% (7/53) and 14% (8/56) respectively. All the remaining patients had either radiological evidence of disease or clinically palpable disease present, before chemotherapy.

Results

Survival related to primary surgery

Eight patients in group A and 25 patients in group B had TAH, BSO with or without omen-

Table 2. Patient characteristics

Patient characteristics	Group A	Group B
Age (years)		
range	33–78	21–75
median	56	55
No. of patients in present study	53	56
FIGO stage		
III	42	48
IV	11	8
Histology		
Mucinous	22	23
Serous	28	30
Endometroid	3	2
Clear cell	0	1
First laparotomy		
TAH, BSO ± omentectomy	8	25
Biopsy	20	15
Partial excision*	25	16

*Any excision less than TAH/BSO but more than a biopsy.

TAH, Total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

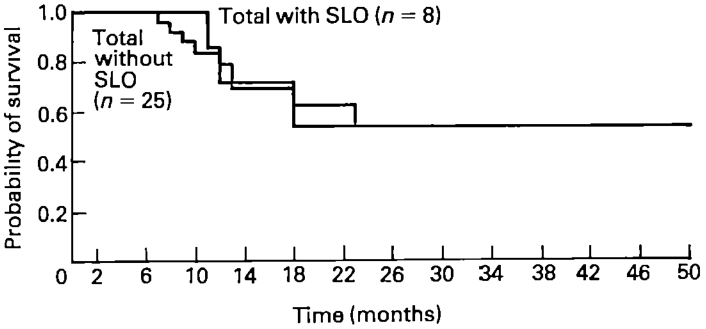

Fig. 1. Survival from diagnosis of patients in group A (with SLO) and group B (without SLO) who had TAH BSO with or without omentectomy at the initial laparotomy ($P<0{\cdot}99$).

tectomy at the initial laparotomy. Of these 25 patients in group B, 13 had complete remission following chemotherapy. The survival in the group who had optimum initial surgery was not significantly different despite additional cytoreductive surgery in group A ($P<0{\cdot}99$) (Fig. 1).

Thirty-five patients had only biopsy of the tumour taken at the laparotomy, 20 in group A and 15 in group B. Only one patient in group A and two in group B had complete remission. The survival in these two groups of patients was similar ($P<0{\cdot}1$) (Fig. 2).

Forty-one patients of the 109 had partial excision of the tumour at the first laparotomy (more than a biopsy but less than TAH/BSO). Twenty-five of these patients had further cytoreductive surgery (group A); of these, five had complete remission prior to SLO. In group B, of the 16 patients who had partial excision of tumour, six had complete remission and none had further cytoreductive surgery. A longer survival was observed in group A ($P<0{\cdot}05$) (Fig. 3).

Survival related to chemotherapeutic response

Of the 53 patients who had an SLO (group A), 42 had a clinical partial response, four had a complete remission and seven had no clinically assessable disease.

Partial responses were seen in 35 of the 56 patients in group B, there were 13 complete responders and eight had no clinically assessable disease.

For the purposes of survival, the patients with clinically unassessable disease have been classed as complete responders.

Survival curves of the partial and complete responders are shown in Figs 4 and 5. There was no statistically significant difference in the survival of patients in complete remission in the two groups ($P<0{\cdot}99$). In the case of the partial responders, the group which had a SLO did marginally better than those who had no further cytoreductive surgery ($P<0{\cdot}005$).

The curves also show that the complete

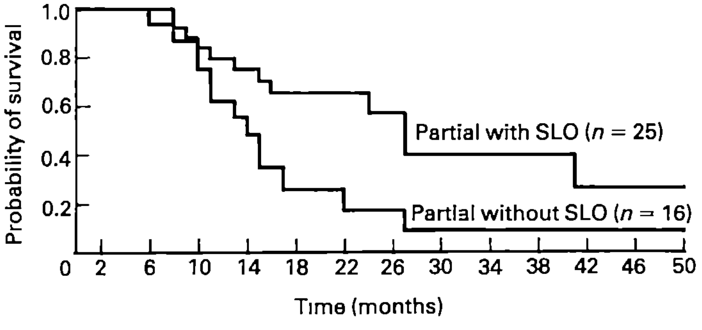

Fig. 2. Survival from diagnosis of patients in groups A and B who had biopsy only at the initial laparotomy ($P<0{\cdot}1$).

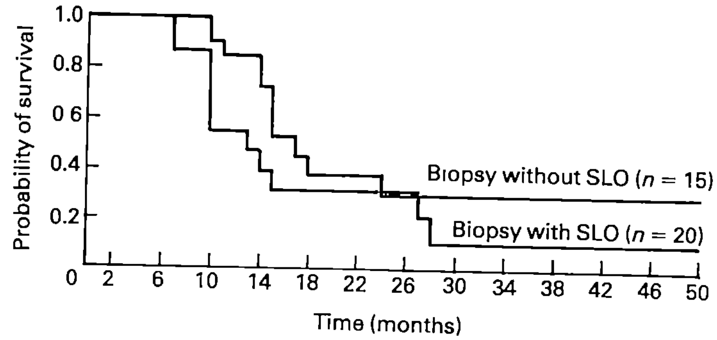

Fig. 3. Survival from diagnosis of patients in groups A and B who had partial excision of tumour (>biopsy but <TAH BSO) at the initial laparotomy (P<0·05).

responders survive longer than those with a clinical partial response.

The overall survival of responding patients with and without further surgery was not significantly different (P<0·99).

Discussion

Whilst there is plenty of evidence to support the idea that survival in advanced ovarian cancer is related to the amount of residual tumour remaining after primary operation (Kaufmann 1966; Munnell 1968; Santesson & Kottmeir 1968), there is little evidence to show that this is due to the diligence of the surgeon rather than the nature of the tumour itself. Indeed, Griffiths *et al.* (1972) have offered convincing evidence that initial bulk resection is of little value unless nearly all gross tumour is removed, and this is only possible where tumour is confined to relatively few areas of the abdomen and pelvis.

In our series of patients, strenuous efforts were not made by the surgeons to remove all tumour at first operation and Figs 1, 2 and 3 show clearly that survival is related to the extent of initial surgery. Thus the median survival for those having TAH and BSO is 23 months, whilst those having a biopsy only had a median survival of 16 months. However, the effect of second surgical removal of tumour is much less clear, in that only in one group (i.e. those who had less than a BSO and TAH but more than a biopsy at initial operation) was there any apparent survival benefit (Fig. 2).

It has been shown many times that the best survival in advanced ovarian cancer is seen in those patients who achieve a complete clinical and surgical response to chemotherapy. It is also known that of those who are in clinical complete remission, a significant proportion will be found to have gross or microscopic disease at second surgery. In a recent study by Stuart *et al.* (1982), 21 patients were thought to be free of disease, but at SLO, six (28·6%) had residual tumour.

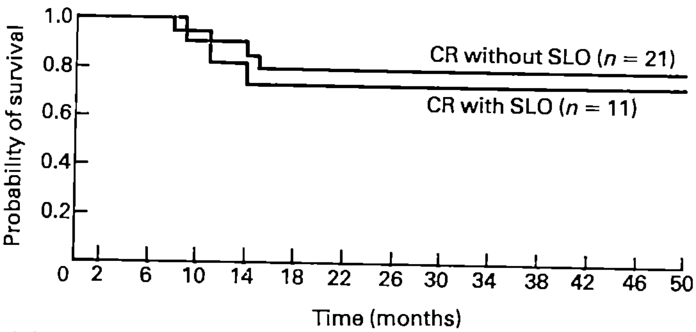

Fig. 4. Relation of complete response following chemotherapy in group A (with SLO) and in group B (without SLO) to survival (P<0·99).

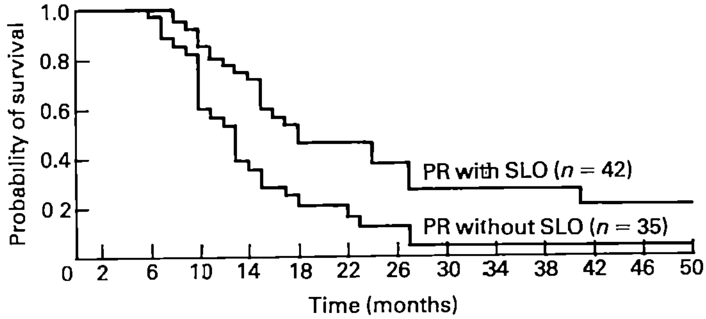

Fig. 5. Relation of patients in partial response following chemotherapy in groups A and B, to survival ($P<0{\cdot}005$)

Indeed, in our earlier study (Raju *et al.* 1982) there were 16 clinical complete responders and none had visible tumour at SLO but four had microscopic disease.

Nevertheless, this undetected disease in patients who did not have SLO in the present study does not seem to have affected survival, since there is no difference in the curves for group A and B cases in clinical complete remission at 5–7 months after initial laparotomy (Fig. 4). But it must be remembered that responding patients continued their chemotherapy for at least 6 months even if they had a surgical or pathological complete remission.

Unexpectedly there does seem to be benefit in further surgery for patients achieving a clinical partial remission even though this surgery very rarely resulted in clearance of residual disease. (Fig. 5).

Smith *et al.* (1972) recommended multiple biopsies at SLO and a change of chemotherapy if residual disease was seen, but in the present study this was not done. In their series, 17·4% of cases had recurrence after negative SLO and Stuart *et al.* (1982) who also did multiple biopsies reported a recurrence rate of 13·3%. In our own series the recurrence rate was 18% in those who had a SLO (group A) and 1% in group B. From these results it is doubtful whether extensive biopsies predict recurrence with greater accuracy than lesser procedures.

It may be considered unreasonable to compare the overall survival of patients in groups A and B because BSO and TAH with or without omentectomy was done in many more cases (45%) in group B compared with 15% in group A, but if initial debulking surgery is of major importance in late-stage ovarian cancer, one would expect a better survival in group B. This was not the case, which would suggest that removal of the ovaries, tubes, uterus and omentum is more a measure of the lower level of aggressiveness of the tumour rather than a measure of the usefulness of surgery. However, there are many factors involved here which cannot be resolved except by randomization.

Nevertheless, our experience suggests that the role of second surgery in the context of modern chemotherapy should be looked at more critically and should be used only in a research setting until its usefulness is better defined. In this spirit we have embarked on a study randomizing patients to second look 'debulking' surgery as part of multi-modality therapy for advanced ovarian cancer.

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Tumour-associated antigen CA 125 in patients with ovarian cancer

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Summary. The serum levels of antigen CA 125 expressed by epithelial ovarian carcinoma were measured in 27 postmenopausal women with ovarian tumours and in 16 controls. Increased serum levels of CA 125 were found in nine (75%) out of 12 patients with ovarian cancer; in three with stage I disease levels were not elevated. No significant difference was found in the concentration of CA 125 detected in peripheral or ovarian venous blood. Decreased antigen levels were found 6–30 weeks after radical operation and cytostatic chemotherapy in the ovarian cancer group. The results indicate the value of measuring CA 125 as a tumour marker in the follow-up of ovarian cancer.

Among gynaecological malignancies ovarian cancer is a major diagnostic problem. Recently Bast *et al.* (1981) discovered a circulating antigen expressed by human ovarian carcinoma cells. Moreover, they demonstrated that the concentration of this antigen, cancer antigen 125 (CA 125), is increased in the serum of 82% of women with epithelial ovarian cancer (Bast *et al.* 1983).

We have further investigated the value of CA 125 in detecting ovarian cancer by measuring it in peripheral and ovarian venous blood in women with benign, borderline malignant or malignant ovarian tumours. In addition, we assessed the response of serum CA 125 to the treatment of ovarian cancer.

Patients and methods

The study group consisted of 27 postmenopausal women (mean age 64 years, range 48–81 years) with ovarian tumours. Thirteen patients had ovarian cancer, according to the international classification (FIGO): three had stage I, two stage II, four stage III and four had stage IV. In all cases the type of ovarian cancer was verified histologically; 12 were of epithelial origin: two mucinous adenocarcinoma, four serous adenocarcinoma, two endometrioid adenocarcinoma, three poorly differentiated adenocarcinoma and one a malignant Brenner tumour, and one was of non-epithelial origin (histiocytic lymphoma). Borderline malignancy of the ovarian tumour was revealed in four (two serous and two mucinous cystadenomas). Of 10 benign ovarian tumours, five were mucinous cystadenomas, one a serous cystadenoma and four undifferentiated cysts. In addition to the study group, the control group consisted of 16 postmenopausal women (mean age 65, range 51–80 years) without ovarian neoplasm who required an operation for uterine myomas or genital prolapse.

Hysterectomy with bilateral salpingo-oophorectomy was performed in all patients with ovarian tumours; in those with cancer as much of the tumour as was safely possible was removed on laparotomy, and in clinical stages III and IV omentectomy was also undertaken. The patients with ovarian cancer received combined cytostatic chemotherapy (adriamycin 40 mg/m^2

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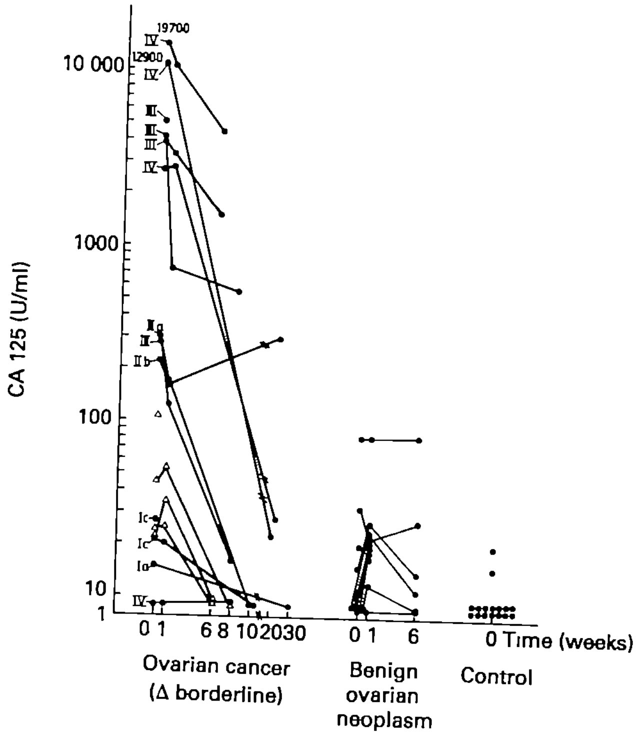

Fig. 1. Serum levels of CA 125 before and after treatment in patients with malignant, borderline or benign ovarian tumours and in controls

+ cyclophosphamide 500 mg/m^2 + cis-platinum 50 mg/m^2 or tegaphur 800 mg/m^2) 1 week after operation and then at intervals of 5 weeks. One patient (stage IIa) also received pelvic irradiation. One patient (stage IIb) refused any additional treatment after operation.

Peripheral venous blood samples were collected the day before the operation and 1 week and 6–30 weeks postoperatively. In addition, another blood sample was taken from the ovarian vein during laparotomy on the side of the tumour in six cases with ovarian cancer, three with borderline malignant ovarian tumour, and seven with benign ovarian tumour.

Measurement of CA 125

We measured CA 125 utilizing the Cancer Antigen 125 Radioimmunoassay kit (Centocor Inc., Malvern, Pennsylvania, USA) according to the instructions of the manufacturer. We observed a hook effect with CA 125 concentrations >3000 U/ml. Our highest specimen (19 700 U/ml) gave a value of 400 U/ml in the initial assay of the undiluted specimen. To avoid misleading results we therefore initially analysed all samples both undiluted and as a 1:10 dilution. The coefficient of intra- and inter-assay variations were 18% and 12·6% respectively. In the sera of 16 healthy non-pregnant women (age 35–65 years) the concentration of CA 125 was <50 U/ml.

Results

Of the 12 patients with epithelial ovarian carcinoma nine (75%) had increased peripheral blood CA 125 concentration, ranging from 300 to 19 700 U/ml (Fig. 1). The clinical stage of ovarian cancer was related to the measured levels: in all three patients with unelevated levels of CA 125 (15, 21 and 27 U/ml) the cancer was in stage I. The patient with non-epithelial ovarian carcinoma (histiocytic lymphoma, stage IV) had a CA 125 concentration of <7·4 U/ml.

Radical operation of the malignant ovarian tumours resulted in decreased levels of CA 125 (to a mean of 51% of pre-operative values) after 1 week in every patient. A further decrease took

Table 1. Peripheral and ovarian venous blood concentration of CA 125 in women with benign or malignant ovarian tumours

Ovarian neoplasm	CA 125 (U/ml)	
	Peripheral vein	Ovarian vein
Ovarian cancer		
1. Mucinous cystadenocarcinoma (Ic)	21	20
2. Mucinous cystadenoca (IIa)	300	260
3. Malignant Brenner tumour (III)	290	270
4. Serous cystadenoca (III)	4000	4050
5. Endometrioid adenoca (IV)	19 700	15 000
6. Histiocytic lymphoma (IV)*	<7·4	<7·4
Borderline malignant		
1. Mucinous cystadenoma	24	16
2. Mucinous cystadenoma	22	24
3. Serous cystadenoma	45	54
Benign ovarian tumour		
1. Mucinous cystadenoma	84	86
2. Mucinous cystadenoma	20	16
3. Mucinous cystadenoma	<7·4	13
4. Mucinous cystadenoma	15	<7·4
5. Serous cystadenoma	<7·4	<7·4
6. Benign ovarian cyst	7·5	27
7. Benign ovarian cyst	<7·4	44

* non-epithelial ovarian carcinoma.

place during the following 6–30 weeks (to a mean 9% of pre-operative values, Fig. 1). In only one case was the concentration of CA 125 increased: from 220 U/ml pre-operatively to 300 U/ml measured 22 weeks after operation. This patient (stage IIb ovarian cancer) was the only one who did not receive any chemotherapy after operation, and progress of the cancer was found upon clinical examination. In other cases the disease status was unchanged or regressed. It is noteworthy that in advanced ovarian carcinomas (stage III and IV) the antigen levels were still high (ranged 125–11750 U/ml) one week after operation and high levels (16, 550, 1100, 4450 U/ml) were also measured 6–8 weeks after operation. In two samples taken at 20 and 22 weeks postoperatively the concentration of CA 125 was low (22, 28 U/ml).

One of the four patients with borderline malignant ovarian tumour had a slightly increased level of CA 125 (107 U/ml). One of the 10 patients with benign ovarian tumour also had a slightly increased value (84 U/ml), which remained constant after operation. All of our 16 control patients without ovarian neoplasm had antigen levels within the reference range (<35 U/ml) given by the manufacturer (Fig. 1).

No significant difference was observed in the concentration of CA 125 in samples taken from peripheral blood or ovarian venous blood (Table 1).

Discussion

In the present series increased serum levels of CA 125 were found in 75% of all epithelial ovarian carcinomas. This accords well with the data of Bast *et al.* (1983). All three ovarian cancer patients with unelevated CA 125 had local ovarian cancer without metastases, whereas in all cases with more advanced disease the levels were over 200 U/ml. In only one out of 10 patients with a benign ovarian tumour did the antigen level exceed the given reference limit 35 U/ml. This suggests that while serum CA 125 may be a specific marker for epithelial ovarian cancer, it may not reveal the disease in its early phase.

It has been demonstrated by indirect

immunofluorescence technique that the murine monoclonal antibody used in this assay has no reactivity with antigen in sections from mucinous ovarian tumours (Kabawat *et al.* 1983). In the present series one patient with stage I mucinous adenocarcinoma had a low serum level of CA 125 (21 U/ml), while the other with stage II had 300 U/ml. This finding also indicates that metastatic mucinous adenocarcinoma may be detected by this assay.

Measurement of CA 125 1 week after radical operation revealed a decreasing trend, although the concentrations were often still very high. This may reflect a long half-time of the antigen, or the production of the antigen from metastases.

In all cases with ovarian cancer there was response to cytostatic treatment and no progression was reported during follow-up. However, in metastasing cases of ovarian cancer the serum levels of CA 125 were still high 6 and 8 weeks after the operation, although significantly lower than before treatment. This suggests that serum CA 125 reflects the amount of tumour mass in the body, and further supports the view of the importance of measurement of CA 125 as a tumour marker in the follow-up of ovarian cancer.

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Plasmapheresis in a pregnancy complicated by acute systemic lupus erythematosis. Case report

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Case report

A 28-year-old woman (para 1+0) was well until summer 1982 when she developed arthralgia affecting the hands, knees and right hip associated with generalized early morning stiffness and Raynaud's phenomenon. She made an unsatisfactory response to non-steroidal anti-inflammatory drugs and was referred to the rheumatology services in 1983. Investigation at that time revealed a positive rheumatoid factor and ANF and antibodies to the extractable nuclear antigens Sm and RNP. Plasma urea and electrolytes were normal. X-rays showed a non-erosive arthritis. A diagnosis of systemic lupus erythematosis (SLE) was made but treatment was not started as the patient had become pregnant.

At 18 weeks gestation she was admitted to hospital with a 10-day history of severe sore throat. There was marked ulceration of the fauces, facial oedema, vasculitic lesions of the finger pulp and generalized erythematous rash. Haemoglobin was 9·8 g/dl with normal red cell indices. WBC was 5·8 × 10^9/l (3% myelocytes). ESR was 39 mm/h. C_3, C_4 and CH50 levels were depressed. Circulating immune complexes (CIC) were detected and antibody titre to native DNA (a-dsDNA) was raised. Plasma urea was 12·0 mmol/l, creatinine clearance was 17 ml/min and urinary excretion of protein was 0·6 g/24 h. Red cell casts were present in the urinary sediment. Renal biopsy showed a diffuse proliferative glomerulonephritis characteristic of SLE.

Treatment was initiated with prednisolone 60 mg daily and the dose reduced after 2 weeks to 40 mg daily. There was slight improvement in wellbeing and creatinine clearance and C_3 levels rose (Fig. 1). The patient continued, however, to have haematuria and proteinuria, an increasingly severe normochromic, normocytic anaemia, detectable CIC and elevated titres of a-dsDNA. An incapacitating proximal myopathy developed 4 weeks after starting steroids. Muscle biopsy suggested a vasculitis. Because of this evidence of continuing disease activity and because fetal growth appeared to be retarded, plasma exchange was commenced after 6 weeks steroid therapy as 4-litre exchanges three times weekly. There was a striking improvement in the myopathy within two exchanges and CIC and a-dsDNA were cleared from the plasma (Fig. 1). Intermittent plasma exchange was continued for 6 weeks and the dose of prednisolone gradually reduced to 30 mg daily. The patient maintained her clinical improvement although the fetus was still thought to be growth retarded. A healthy male child (1 8 kg) was born by elective caesarean section at 32 weeks. Steroids were briefly increased in the postpartum period to 60 mg/day and reduced after 10 days to 40 mg/day. One further plasma exchange was performed. The dose of prednisolone was reduced during the following weeks to a maintenance of 20 mg/day. Three months later the child continues to grow normally. The mother has again developed signs of active disease with detectable CIC and haematuria but a normal creatinine clearance.

Discussion

Plasmapheresis in combination with steroids or cytotoxic agents has been reported as a useful treatment for patients with SLE (Verrier-Jones *et al*, 1979) although not yet firmly established to to be more effective than drugs alone. A recent

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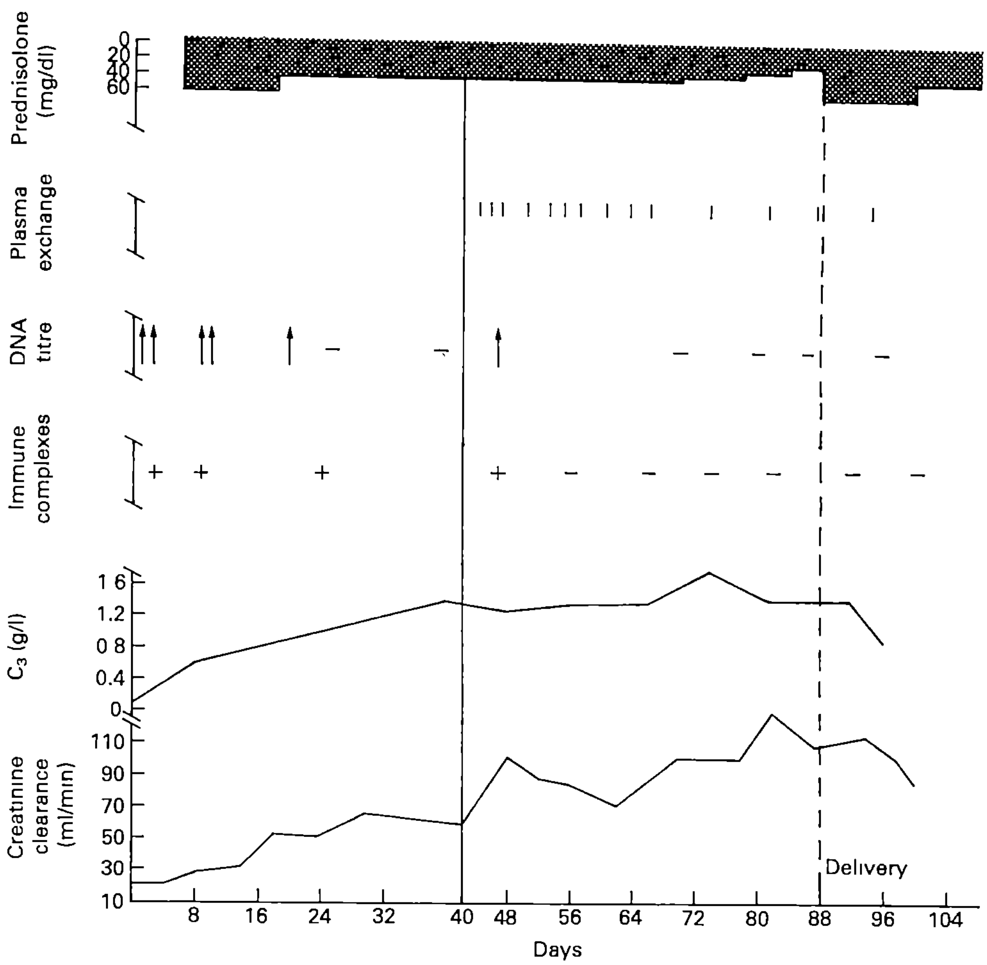

Fig. 1. Creatinine clearance and laboratory measurements in relation to treatment with prednisolone and plasmapheresis.

review suggests that 80% of patients will derive at least transitory benefit from addition of plasma exchange and will not suffer clinical or immunological rebound associated with the use of plasmapheresis alone (Vernier-Jones 1982). The symptomatic improvement in our patient was closely related to the initiation of plasma exchange and would support this contention. There is very little information on the use of plasmapheresis during pregnancy (Hubbard Portnoy, 1979). The incidence of spontaneous abortion in SLE remains as high as 46% in mothers with active disease and is unaffected by steroid therapy (Fraga *et al.* 1974). Although immune complexes have never been demonstrated in the placenta, spontaneous abortion has been associated with decidual vasculitis and the persistence of lymphocytoxic antibodies (Zurier 1980). Plasma exchange is therefore of theoretical benefit. We have shown that plasmapheresis in pregnancy can be performed safely and further studies are required to validate its use as an adjunct to chemotherapy.

Acknowledgment

We wish to acknowledge the help of Professor G Nuki. We would also like to thank Dr Mary Macdonald, Department of Pathology, University of Edinburgh, for reporting the renal biopsy, and Blood Transfusion Service, Royal Infirmary, Edinburgh, for carrying out plasmapheresis.

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Condylomatous atypia of the endometrial cavity. Case report

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Case report

The patient, a 46-year-old housewife and ex-factory cleaner, presented 3½ years ago with a lump of 3 years' duration on the left labium which had recently been painful. She was married, para 2 + 1 and her last menstrual period had been at 38 years of age. A sheath was used for contraception. There was no significant previous medical history. Examination revealed a 25-mm diameter warty tumour of the left labium and a white plaque on the posterior lip of the cervix. The labial tumour proved to be a condyloma acuminatum, the posterior lip of cervix showed a flat condyloma and the anterior lip showed cervical intraepithelial neoplasia, grade 2 (CIN 2) with koilocytotic atypia.

She was subsequently treated by cryoprobe applications to the cervix and repeated cervical cytology screening, the latter showing persistent koilocytotic atypia. After 2 years during which she failed to attend for further treatment, the patient finally presented with a 6-month history of an offensive, creamy, non-blood-stained vaginal discharge. Speculum examination revealed normal labia and vagina and a white plaque on the anterior lip of the cervix. Biopsies of the cervix showed a flat condyloma acuminatum with koilocytotic atypia and associated foci of CIN 3 in the endocervical canal and glands. In view of these findings, a simple hysterectomy was performed. At operation, the endocervical canal was narrowed and some pus-like material escaped from the endometrial cavity.

Pathological examination of the uterus showed some superficial ulceration of the ectocervix. The mucosa of the narrowed endocervical canal and the mucosa of the endometrium were thickened, white and warty (Fig. 1). The myometrium was normal. Microscopic examina-

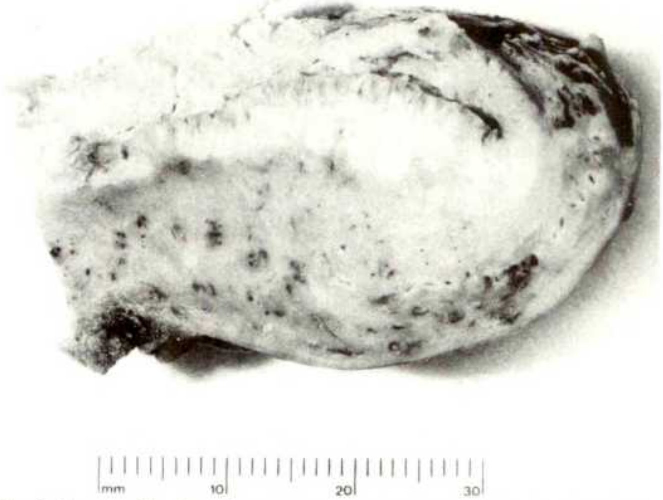

Fig. 1. Longitudinal section of uterine body and upper part of endocervical canal showing a white, warty, thickened endometrium and endocervical mucosa.

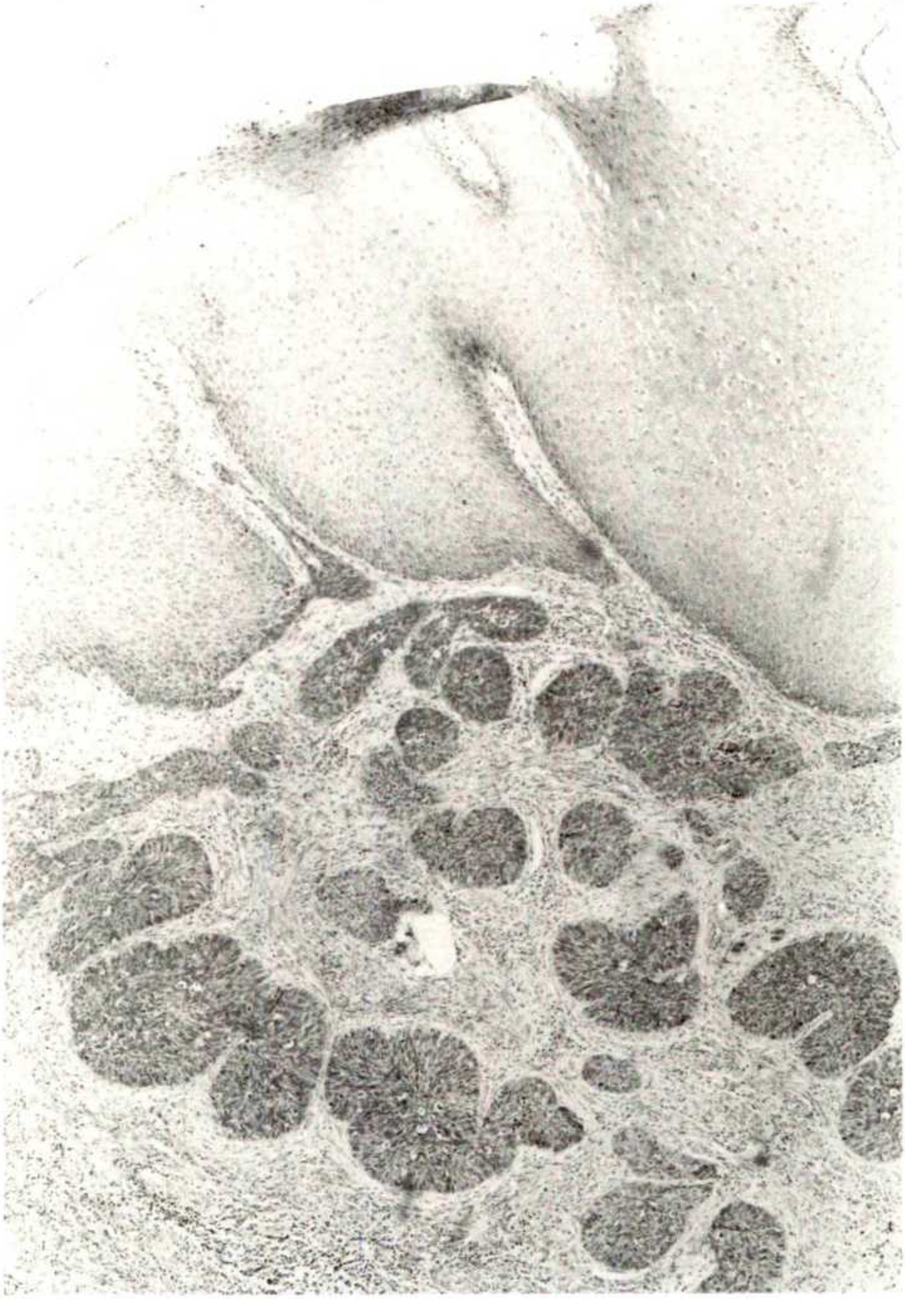

Fig. 2. Condyloma acuminatum with koilocytotic atypia of endocervical canal and underlying invasive squamous carcinoma. Haematoxylin and eosin ×50.

tion of radial blocks of the cervix showed CIN 3 with a condyloma acuminatum, and adjacent occult infiltrating squamous carcinoma in the endocervical canal (Fig. 2). The carcinoma had invaded one-third of the thickness of the endocervical muscle wall. Not only had the condylomatous atypia replaced the lining of the endocervical canal, but it had also almost completely replaced the lining of the endometrial cavity and associated glands with stratified squamous mucosa (Fig. 3). The metaplastic mucosa showed superficial keratinization and atypia with bi-nucleated squamous cells and koilocytosis strongly suggestive of condyloma

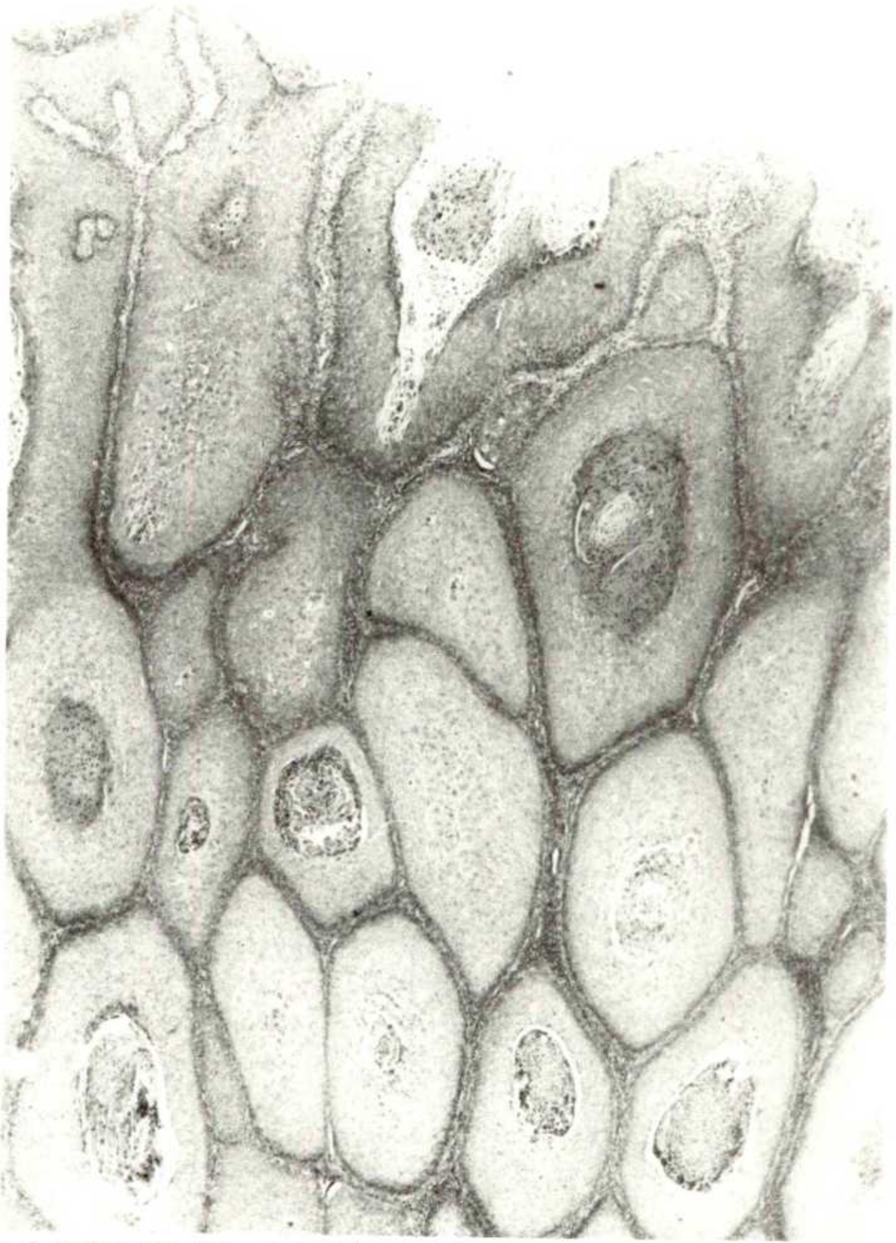

Fig. 3. Replacement of the whole thickness of the endometrial glands by koilocytotic stratified squamous mucosa of condylomatous type. Haematoxylin and eosin ×50.

wart virus infection (Fig. 4). Only a few of the endometrial glands of the basalis showed residual glandular epithelium. No invasion was seen.

Discussion

Among the risk factors associated with squamous carcinoma of the cervix, several types of human papilloma virus which cause overt or subclinical condyloma acuminatum have become increasingly important agents eclipsing the role of genital herpes virus (Reid *et al.* 1982; Morris *et al.* 1983; Singer *et al.* 1984). This patient illustrates not only this well-recognized association, but also shows what we believe to be a unique example of areas of condylomatous atypia

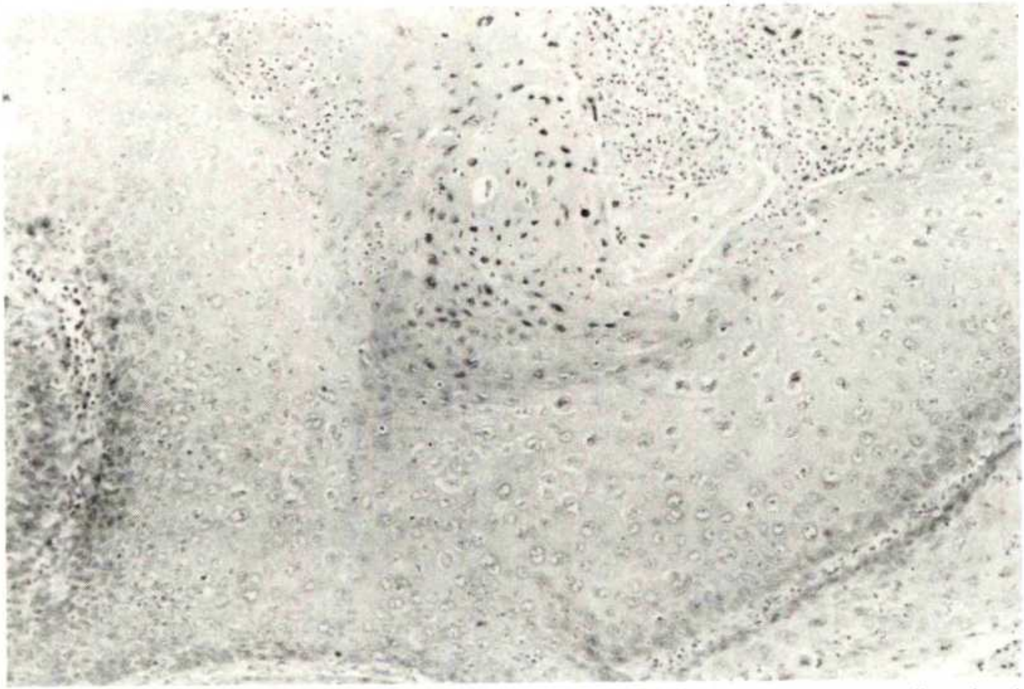

Fig. 4. Detail of the koilocytotic stratified squamous mucosa of the endometrial cavity. Haematoxylin and eosin ×95.

extending from the vulva to the endometrium. We do not know of an example in the literature of such striking replacement of endometrial glands by atypical koilocytotic stratified squamous mucosa, an appearance which is quite distinct from the type of squamous metaplasia associated with a pyometra. The cessation of menstruation at the age of 38 years suggests that the process affecting the endometrium may have been present for many years. Baggish & Woodruff (1967), in their comprehensive review of the occurrence of squamous epithelium in the endometrium, cited several examples of an invasive squamous carcinoma of the cervix associated with in-situ and invasive squamous carcinoma of the endometrium. There is, however, only one report of invasive squamous carcinoma of the cervix with in-situ squamous carcinoma in the endometrial cavity (Friedell 1958). There is no mention of any associated condylomatous change.

Our patient differs from the one described by Friedell (1958) in that only the condylomatous atypia replaced the endometrial glands not the invasive element of the squamous carcinoma of the cervix, the latter being morphologically distinct. We can only speculate whether the atypical squamous mucosa in the endometrium would have transformed into an invasive squamous carcinoma.

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Spontaneous rupture of the liver in association with pregnancy. Case report

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Case report

A 34-year-old woman whose only previous pregnancy had ended in a caesarean section was admitted at 38 weeks with weak irregular contractions. The pregnancy had been uneventful and the blood pressure normal.

She had had mild epigastric pain for the previous 2 weeks. There had been no trauma. Mild epigastric pain recurred intermittently, but there were no abnormalities on examination.

Four days after admission, whilst lying quietly, she had sudden severe epigastric pain radiating to the right shoulder, and collapsed. The heart rate was 88/min, the systolic blood pressure was 60 mmHg, the abdomen was soft with no tenderness or abnormal masses and normal bowel sounds. The uterus was soft and nontender and the fetal heart rate about 80 beats/min. There was no vaginal or rectal bleeding. A chest X-ray was normal and an ECG showed right heart strain. The initial haemoglobin level was 11·6 g/dl but 30 min later it had fallen to 6·6 g/dl due to resuscitation with plasma expanders. The platelet count was 40 000/μl. This was thought to be attributed to consumption; and there was no evidence of haemolysis. Ultrasound showed a large amount of free peritoneal fluid in which loops of bowel were floating. There was no fetal heart movement.

At laparotomy the peritoneal cavity was seen to contain a large volume of blood. The uterus was intact but there was a rupture in the superior surface of the right lobe of the liver with a large subcapsular haematoma. A caesarean section was performed and a stillborn infant extracted. The haemoperitoneum was evacuated.

Persistent bleeding from the liver surface was controlled by temporary placing of surgical packs on the disrupted surface (the right lobe of the liver) and applying bimanual pressure. Bleeding was arrested and four large 'Redi-Vac' suction drains were inserted. A total of 15 units of blood and 5 units of fresh frozen plasma was transfused.

Subsequently recovery was uneventful. The four drains were removed at 8, 10, 12 and 28 days after operation respectively. In an attempt to determine the nature of any underlying pathology both radioistope and ultrasound scans of the liver were performed in the puerperium. The liver substance appeared normal. A collection of fluid corresponding to the site of the subcapsular haematoma was detected on both scans.

The patient returned home 31 days after operation

Discussion

Spontaneous rupture of the liver is a rare complication of pre-eclampsia and is extremely unusual in association with normal pregnancy. The condition has a reported overall mortality rate of 59% for the mother and 62% for the fetus. The true prevalence is unknown but has been reported as varying from 1 in 40 000 to 1 in 250 000 deliveries. The aetiology remains poorly understood. Fewer than 100 cases have been reported, the majority in hypertensive women with or without hypofibrinogenaemia.

The condition should be regarded as a surgical emergency requiring resuscitation and surgical intervention. Direct attack upon the liver should be avoided because of its friability and vascularity. Suturing may cause further damage and aggravate the bleeding. Bimanual compression and application of local haemostatics whilst replacing blood and clotting factors may be of benefit whilst clamping the portal triad between the index and the thumb as suggested by Pringle (1908) is useful in reducing the rate of bleeding. At times, however, a vascular clamp on the portal triad can be used to achieve temporary haemostasis (Little 1971). It has been shown that normothermic ischaemia of the liver can be extended beyond the generally accepted 15 min when necessary (Huguet *et al.* 1978). Patcher & Spencer (1979) described the different methods of arresting liver haemorrhage and debridment.

We suggest the use of a closed system suction drainage using a negative pressure of 20 mmHg as a result of our experience with the reported patient.

Spontaneous rupture of the liver was first reported by Abercrombie (1844). The patient was 35 years old and collapsed 26 h after delivery, postmortem showed a soft liver with two lacerations and haemoperitoneum. In an excellent review and report of two patients by Bis & Waxman (1976), the pathology was discussed but the aetiology remains unknown Golan & White (1979) reported five patients of whom three survived, it is suggested that a slight external trauma unrecognized by the patient, or an endogenous trauma could be the aetiological factor causing the rupture The most common presumptive diagnosis was ruptured uterus or placental abruption although in the majority the diagnosis was not made until laparotomy or post mortem.

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SHORT COMMUNICATIONS

Campylobacter carriage and pregnancy

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Campylobacter jejuni and *Campylobacter coli* are prevalent causes of acute bacterial gastroenteritis. Although campylobacter enteritis is recognized in the neonatal period the carriage rate of *C. jejuni/coli* in women during labour and the subsequent transmission rate from mother to baby during delivery have not been determined.

Patients and methods

Rectal swabs were collected from consecutive women in labour attending Fazakerley Hospital, Liverpool during a 4½-year period commencing in January 1980. Swabs were placed in Stuart's transport medium and delivered to the laboratory Stool specimens were sent from women complaining of diarrhoea during pregnancy and where possible from babies born to infected mothers. Specimens were processed using standard techniques.

Results

During the survey period 12 521 rectal swabs were received from the labour suite. Twenty-eight yielded *C. jejuni/coli* (0·2%) and 24 of these were from women who had no gastrointestinal disturbance during delivery nor in the postpartum period. One of these paients had been admitted earlier with a provisional diagnosis of ectopic pregnancy but campylobacter infection, manifested by diarrhoea and abdominal pain, was eventually diagnosed. The remaining four women had diarrhoea immediately before, or soon after, delivery and in one this precipitated labour at 36 weeks gestation. Another woman suffered gastrointestinal upset at 36 weeks gestation when premature labour was a differential diagnosis but carriage of the organism had ceased by term.

Of 15 stool specimens from babies, all born vaginally, only two (13%) yielded campylobacters (Table 1).

Discussion

C. jejuni/coli is not part of the normal vaginal flora as shown by studies in asymptomatic (Blaser *et al.* 1980) and unselected women (Wright 1983). In this present study, vaginal swabs from the mothers of the infected newborn infants were not submitted specifically for examination of *C. jejuni/coli.* However, there has been one report (Anders *et al.* 1981) of a positive culture from a high vaginal swab in a woman whose baby developed enteritis soon after birth and another from a cervical swab taken from a woman with a history of abdominal pain and diarrhoea in the previous month (Wright *et al.* 1982).

It is possible that the two babies with evidence of transmission of *C jejuni* from mother to baby (Table 1) ingested the organisms (of either faecal or vaginal origin) during vaginal delivery. It is known that the adult infective dose can be as low as 500 organisms (Robinson 1981) and it may be lower in the newborn. Coid & Fox (1983) suggested that during acute *C. jejuni* infection in pregnant women the organism is likely to be localized in the placenta. They described the abnormal histological findings in a placenta from a bacteraemic woman who had a second-trimester abortion apparently precipitated by *C jejuni* infection However, they did not mention histological features of the fetus nor postulate whether transplacental infection might have occurred. Infection by this route is thought unlikely in the two patients described here as the babies were never clinically septicaemic even when gastrointestinal disturbance developed and the placentas were macroscopically normal.

Campylobacter enteritis during pregnancy

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Table 1. Transmission of *Campylobacter jejuni/coli* from mother to baby

Intrapartum *Campylobacter* carriers (n = 28)	Babies			
	No. at risk	No screened for *C jejuni/coli*	No positive	Clinical features
Symptomatic	4	2	1	Blood and mucus in stool, anal fissure
Asymptomatic	24	13	1	Watery stools mixed with blood and mucus, red and friable rectal mucosa

can present a diagnostic problem as it is often manifested not only by diarrhoea, often bloody, but also vomiting, abdominal pain and systemic disturbance. In contrast, infection in the newborn usually appears to be manifested only by the passage of blood and mucus per rectum in an otherwise healthy baby (Anders *et al.* 1981). campylobacter enteritis in newborn babies with these signs should be considered even in the absence of maternal symptoms.

The rectal carriage rate of *C. jejuni/coli* in this asymptomatic pregnant group was 0·2%, while other authors have reported rates of 0–1·6% in populations of mixed ages in the United Kingdom (Skirrow 1977; Dale 1977; Tanner & Bullin 1977; Telfer Brunton & Heggie 1977). The small numbers reported here may be explained by the examination of rectal swabs as opposed to stool specimens.

Acknowledgments

We are grateful to our Consultant Obstetrician, colleagues Mr J. Barr, Mr P. Rae, Mr K. Perera and Mr P. Bousefield and their staff for their interest and support.

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BOOK REVIEWS

Progress in Obstetrics and Gynaecology Volume 4, edited by John Studd. Churchill Livingstone, Edinburgh, 1984, 394 pages with figures and tables, £15.00

John Studd's fourth volume in this series shows no slackening of pace nor lack of interesting subjects whose progress we should be informed about. I note with regret the absence in this issue of John Studd's 'leader style' preface, in which concepts and institutions are taken to task. In this volume, our attention is focussed firstly on general topics which are important—the relation between the gynaecologist and the patient and the medico-legal aspects of our speciality. The first chapter is directed more towards the male gynaecologist of whom much more is expected nowadays in terms of understanding his female patients, her fears and aspirations. This Chapter needed a much deeper exploration with less emphasis on clichés like 'the classic position of the male physician: paternalistic and sympathetic but stand-offish'. There needed to be a greater discussion of the female personality both seen as a patient and in the perspective of the changing role of women in our society. Margaret Puxton's well-written chapter on medico-legal aspects is an important warning to us all, that our patients are taking us increasingly into the arena of the courts. I would like to have read more about the legal position of failed sterilization and how practitioners can protect themselves once this has occurred. The obstetrical choices are topical. The chapter on IUGR had obviously gone to press before the recent finding that it was likely to be due to psychosocial stress as well as cigarette intake. Malcolm Pearce and Stuart Campbell have produced a comprehensive chapter on ultrasound: because of the present controversy and public interest over its safety, space should have been given to discuss the biological effects of ultrasound and why they are unlikely to be relevant or harmful when used for obstetrical purposes. Norman Beischer and colleagues in their chapter on IUGR, suggested that we still need the full range of biophysical and biochemical 'placental tests' and that the urinary oestriol measurement is still with us. As yet, no other test stands supreme and that is poor progress indeed. It is of no surprise to read that eclampsia is still treated with magnesium sulphate in the USA, yet it is rarely used here—that cannot just be English xenophobia: surely there needs to be a well-controlled trial between magnesium sulphate and our choice agent here. Sakomoto and colleagues succinctly describe the technique of radical abdominal hysterectomy but used poor figures to illustrate their surgery. I was surprised to see that urethral catheterization with its attendant archaic management, was preferred to the suprapubic method. The remaining gynaecological section is notable for a lucid explanation of the steroid chemistry of PCO by Gillian Lachelin, a frank and comprehensive review of the premenstrual syndrome by Adam Magos and the editor, and a practical chapter on sexually transmitted diseases of the vulva by Hilary Lavery. That there may not be any apparent direction or sequence of the topics chosen for each volume, is I think irrelevant. John Studd's simple formula of sending each volume to press when a balance of sufficient contributions have been received, ensures that there is a new and up-to-date volume each year. He maintains the ability to select interesting authors in the van of progress and, as shown here, takes us outside the narrow confines of our speciality. More please. *Progress in Obstetrics and Gynaecology* must now rank as one of the major series to keep examination candidates and practising obstetricians and gynaecologists up to date, both here and abroad.

Stuart Stanton

Drug Treatment in Gynaecology R. S. Ledward. Butterworths, Sevenoaks, Kent, 1984, 184 pages with figures and tables, £7.95

This light, pocket-size, paperback book is a handy gynaecological formulary which presents prescribing information on drugs commonly used, or encountered, in everyday gynaecological practice. The 12 sections comprise the main symptom and pathology complexes starting with the banal but ubiquitous vaginal discharge.

Other headings under which the drugs in the therapeutic armoury are classified include pelvic infections, infertility, pregnancy termination, lactation suppression and fertility control, premenstrual syndrome, the climacteric, gynaecological malignancies and terminal care. Each section begins with an introduction, which in a small volume is necessarily quite superficial in its approach to the subject. The description of drugs includes the approved name, dose, contraindications, side-effects and special features. Inclusion of proprietary names in the text would have appealed to many readers but these are given in the drug index and glossary at the back of the book, before the subject index. Each section ends with a brief summary or note on the choice of preparation and there is also a short list of works for further reading. It is a pity that several errors have found their way into the final print. These are mostly obvious enough to be inconsequential, for example 'Oxytocin 50 l/u in 5% dextrose . . .' (p. 65) but dosage of prostaglandin E_2 expressed as mg instead of μg per minute could mislead (p. 61). Bethanechol, carbachol and distigmine bromide are erroneously listed as anticholinergic drugs (p. 136). This book will find a useful place as an economical quick reference source on gynaecological wards and in the coat pockets of senior house officers in gynaecology.

Roy Husemeyer

Books received some of which will be reviewed at a later date

Prevention of Physical and Mental Congenital Defects, Part A: The Scope of the Problem (Progress in Clinical and Biological Research. Vol. 163A), edited by Maurice Marois. Alan R. Liss Inc New York, 225 pages with figures and tables, £41 00

Die Gebarthaltung der Frau (The Delivery Position of Women Historical, anthropological and medicinal studies on pregnancy and birth) by Liselotte Kuntner Hans Marseille Verlag GmbH, Munchen, 1985, 205 pages, fully illustrated, DM 48

The Parents' A to Z..A Guide to Children's Health Growth and Happiness by Penelope Leach. Penguin Books Ltd, London, 736 pages, £6.95

Cancer of the Uterine Cervix. Actual Problems of Screen Programs (Cancer Campaign Vol. 8.) edited by H. G Bender & L Beck. Gustav Fisher Verlag, Stuttgart, 1985, 231 pages with figures and tables, DM 110

Clinics in Obstetrics and Gynaecology Vol 11 No 3. Contraception Update edited by John R Newton. W. B. Saunders, London, 1984, 260 pages fully illustrated, £12.50

Laser Surgery in Gynecology and Obstetrics edited by William R. Keye Jr Castle House Publications, Tunbridge Wells, Kent, 1985, 224 pages, illustrated, £39.50

Bacterial Infections in the Fetus and Newborn Infant (Major Problems in Clinical Pediatrics Vol 26) by Pamela A. Davies & Leif A. Gothefors. W. B. Saunders, London, 1984, 266 pages, illustrated, £37.50

Perspectives on Abortion edited by Paul Sachdev. Scarecrow Press Inc, Metuchen, New Jersey, 1985, 293 pages, $22.50

Research in Perinatal Medicine (II). Fetal Neuroendocrinology (Proceedings of a Symposium Mariensee West Germany 1984), edited by F. Ellendorff, P. D Gluckman & N Parvizi. Perinatology Press, New York, 1984, 285 pages with figures and tables, no price given

Basic Physics and Technology of Medical Diagnostic Ultrasound by Matthew Hussey. Macmillan Ltd, London, 1985, 236 pages with figures and tables, £15 00

Diabetes Mellitus: Achievements and Scepticism (International Congress and Symposium Series No 77), published by The Royal Society of Medicine, 1 Wimpole Street, London, edited by Jane Church. 200 pages with figures and tables, £15.00

Premenstrual Syndrome and Dysmenorrhea edited by M. Y. Dawood, J. L. McGuire & L. M. Demers. Urban & Schwarzenberg, Baltimore 1985, 237 pages with figures and tables, £28.95

Fluids/Electrolytes/Nutrition by Allan Engquist Munksgaard International Ltd, Copenhagen, 1985, 230 pages illustrated, D Kr 135.00

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Tables and figures

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Figures should be marked on the back (light in pencil) with the name(s) of the author(s), the figure number, and the top indicated. Each should have a descriptive legend typed on a sheet separate from the figure. Photographs should be unmounted glossy bromide prints of good contrast.

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Trudinger, B. J., Lewis, P. J. & Petit, B. (1979) Fetal breathing in intrauterine growth retardation. *Br J Obstet Gynaecol* **86**, 432-436.

Hytten, F. E. & Leitch, I. (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p. 26

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Child-bearing, Health and Social Priorities:

A survey of 22 774 Consecutive Hospital Births in Zaria, Northern Nigeria

by

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Child-bearing, Health and Social Priorities: A Survey of 22 774 Consecutive Hospital Births in Zaria, Northern Nigeria

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Dedicated to the memory of William Charles Wallace Nixon CBE (1904–1966) Professor of Obstetrics and Gynaecology University of London at University College Hospital. His teaching and his deeply felt concern for the welfare of pregnant women and children largely inspired this work.

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1. Introduction

Childbearing in most areas of the Third World is a dangerous gamble; mortality rates are often estimated as being of the order of 10 per 1000 deliveries for the mother and 100 per 1000 deliveries for the infant. Deaths on this scale are a direct result both of serious defects in the social, cultural and economic backgrounds, and of inadequacies in the existing health services If maternal and perinatal mortality rates are to be reduced, then a logical first step is to examine the present position in detail. this was attempted at the Department of Obstetrics and Gynaecology, Ahmadu Bello University (ABU) Hospital in Zaria, Northern Nigeria during 1976–1979

The major aim of this study from Zaria was to determine the maternal health care needs for the area based on relations of pregnancy outcome and complications to maternal biosocial variables especially age, parity, physique and education; and to the delivery of health care. Many of the findings described here could well apply to other places in the Third World whose socioeconomic and cultural characteristics are akin to those of Northern Nigeria. But the report goes further: it brings to light the grave risks taken by pregnant women and their babies when they are denied access to orthodox medical care and when they fail to utilize existing orthodox health care services

The report begins with background information on Nigeria as a whole and on Zaria in particular, together with accounts of the existing maternity services and of the conduct of this maternity survey. This is followed by an analysis of the influence of antenatal care and formal education on childbearing. The next three sections concentrate on early teenage pregnancy, highlighting its obstetric complications, stressing the background of these teenage mothers, and then going on to show that during adolescent pregnancy, growth in height occurs particularly among those who are protected against malaria and who also receive iron and folic acid supplements. The section devoted to multiple pregnancy is not exclusive to twins only: triplets, quadruplets and conjoined twins also feature. Congenital malformations seen at birth are briefly presented but detailed analysis was not attempted because conditions of work in Zaria did not permit this and in any case, congenital malformations contribute very little to overall perinatal mortality. Two further sections add to our knowledge of the mode of delivery and highlight the fact that in certain sections of the local community, women delivered by caesarean section and others who had had repair of vesicovaginal fistula fail to return to hospital for care in subsequent pregnancy until they get into trouble during labour The sections devoted to perinatal mortality and maternal mortality go into as much detail as our data would permit. It is in these sections that the health and social priorities for the Zaria area and indeed for the impoverished areas in the Third World become blindingly obvious.

I am most grateful to all who contributed towards the eventual completion of this survey of Zaria births. In particular, I wish to thank the following friends, colleagues, institutions and organisations: Professors O. O. Akinkugbe and I. S. Audu, former Vice-Chancellors of Ahmadu Bello University, Zaria, Professor Umaru Shehu, former Director of the Institute of Health of ABU, Zaria, Professor and Mrs L. G. Egler (Zaria), Irma Seppanen (Vantaa, Finland), Mrs Sue Awunor-Renner (Invercargill, New Zealand), Mr U. Eleanya (Zaria), Mrs Margaret Murphy (Gauci, Spain), Mallam Hassan Dauda (Zaria), Mr Peter Samuels (Cardiff), Dr M. Campbell-Brown (Harrow), members of staff of the following departments at ABU Hospital Zaria. obstetrics and gynaecology, paediatrics, haematology and blood transfusion, medical social services and instrument engineering; members of the staff of the Division of Computing and Statistics and of the Medical Illustration Unit at the Clinical Research Centre, Harrow; and the National Board of Health, Helsinki, Finland.

Throughout the difficulties I always had the support of Sir Christopher Booth, Director of the Clinical Research Centre of the UK Medical Research Council (Harrow) and Dr A. Kessler, former Head of the Special Programme of Research on Human Reproduction, World Health Organization, Geneva.

I thank Mrs Ruth White and Mrs Nicola Wilson Smith for the excellence of their secretarial help.

Imperial Chemical Industries (ICI) and Smith, Kline and French Laboratories Ltd (UK) supplied the drugs used for the work reported in chapter 5; Family Health International (USA) partly funded the computing costs incurred in the preparation of chapters 7, 8, 10 and 12.

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2. Background information

Summary. An account is given of the living conditions both in Zaria and in Nigeria as a whole, including relevant historical and geographical aspects, problems of the economy and food production, and local cultural beliefs. The maternity services are described, followed by accounts of the collection and analysis of the records of all 22 774 consecutive pregnancies, with 22 725 deliveries, at the Department of Obstetrics and Gynaecology, ABU Hospital, Zaria. There were 238 maternal deaths and 2718 perinatal deaths.

An important feature of Nigerian life is the absence of reliable information on the country (Harman 1982). In particular, not much is known about mortality and morbidity associated with child-bearing in most areas of the country. Yet the underlying poverty and the social complexity of the population with its varied ethnic groups, religious beliefs and traditional forms of health care, are bound to have a major influence on reproduction.

Ideally, information about child-bearing in any area should always be sought from records of either births in the total population or a random sample of them. But in the Zaria area, as elsewhere in Nigeria, much of the infrastructure needed for such an exercise is simply not there, so that any survey has to be confined to hospital admissions only. Between 1 January 1976 and 30 June 1979, records were kept of all women who were delivered in Ahmadu Bello University (ABU) Hospital, Zaria, or who were admitted there shortly afterwards, a total of 22 774 pregnancies.

Data on all these women and their newborn infants were initially kept on cards, before eventually being encoded and put into the Clinical Research Centre (Harrow, UK) computer system for analysis.

Because this material is hospital based, purists will insist that the picture which it paints can never be representative of the area. We accept this criticism but at the same time we are convinced that, correctly interpreted, these results could be instrumental in showing which way social, economic, health and even political planning should go

Nigeria

Nigeria, situated at the eastern end of West Africa and with an Atlantic coastline of some 800 km, covers an area of 920 000 km^2 (Fig. 2.1). Its 80 million people speak 394 indigenous languages (Hansford *et al.* 1976) with probably as many ethnic groups, each with its own culture Asiatics and whites constitute a tiny minority (perhaps less than 1%) and they are there temporarily as professionals and employees of various multinational companies. Nigeria's political system is based on a federation of 19 states, headed until recently by an elected president. However, at all levels of government and administration, the demarcation between traditional norms and modern democratic practices is never clear-cut. Vital decisions affecting the well-being of the whole country are not infrequently muddled by compromise, thus creating problems which might never have arisen.

Notwithstanding Nigeria's considerable earnings from the sale of crude oil, and her vast physical and human resources, there is widespread poverty and deprivation. Income per capita is around US$300, with the gap between the rich and poor exceedingly wide Improvements and developments taking place in the country to meet the basic needs of the people, such as housing, food and water supply, health services and education, are slow (Federal Office of Statistics 1983*a*) and are further hindered by an increasing population. Public utilities, telecomunication systems and power supply fall far short of the country's requirement.

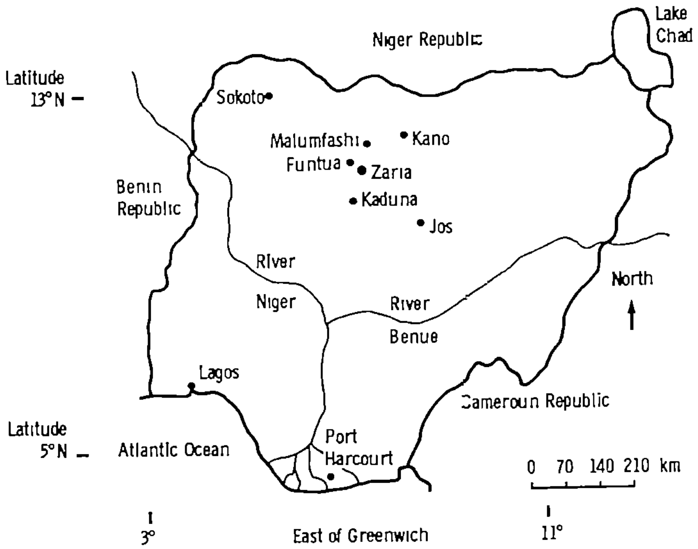

Fig. 2.1. Map of Nigeria

Agricultural production, including forestry and fishing, is the main industry involving about 70% of the active population, yet the farmers in the rural areas remain the poorest in the community Low productivity, heavy crop losses due to infestation and spoilage, and poor marketing systems are some of the factors held responsible for rural poverty (Olatunbosun 1975). Since the Sahel drought of 1973–1974, food production has continued to fall (Federal Office of Statistics 1983*b*) (Fig. 2.2) and the resulting increase in food prices (Fig. 2 3) has led to a decline in the standard of nutrition.

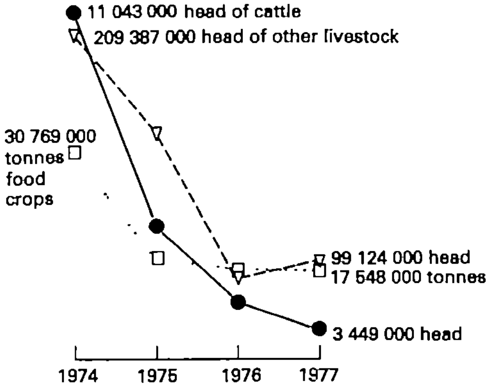

Fig. 2.2. Production of food crops, cattle and other livestock in Nigeria. (In 1978 and 1979, there were 2 47 and 3·22 million head of cattle, 92·02 and 108·46 million head of other livestock, 13·96 and 16·12 million tonnes of food crops)

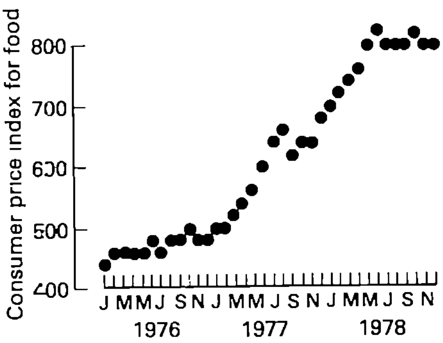

Fig. 2.3 Monthly consumer price indices for food in Zaria 1976–1978 (base average for 1960 = 100).

Zaria

Historical, geographical and socioeconomic features

Zaria is at least six centuries old and during its history there have been three major epochs, the effects of which are still obvious. First, there was Islamization which began in the 14th century and culminated with the Jihad (Islamic Holy War) of 1806 Second, and subsequent to the Jihad, a feudal system of government with an Emir as ruler was imposed. The basic structure of this system remains preserved. The last of the three major epochs was British colonial rule from 1903 to 1960.

Zaria, on the vast Guinea savannah forest belt which covers nearly one-third of Nigeria, is linked by road, rail and air to Lagos, the capital, some 900 km to the south The climate is tropical, being hot and dry with an annual wet season from May to September, during which some 1000 mm of rain falls. Once the rainy season begins, soil preparation and cultivation start, mostly by simple traditional hand tools. Among the food crops grown are millet, guinea corn, maize, yams, potatoes, sweet potatoes, cassava, cowpeas and rice Vegetables include onions, pepper, tomatoes and okro. Groundnuts and cotton are the main cash crops. In traditional Hausa society in Zaria, only males farm. Women are semi-secluded and take little part; instead they work inside compounds processing food for domestic consumption and for sale. Nomadic Fulanis keep cattle, but meat production and milk yield from this source are poor

The rainy season is the time of food scarcity and it is during this period that malaria transmission and parasitaemia are highest, and diarrhoeal diseases, measles and guinea worm reach their peak. Epidemics of meningococcal meningitis occur annually around February to April.

Zaria and its environs support an estimated population of 200 000 most of whom are farmers, traders, craftsmen, small-scale businessmen, clerical workers and cattle rearers. Hausas and Fulanis, who together form more than half of the population, are the indigenes and the rest come from nearly 120 other Nigerian ethnic groups. Important differences exist between the indigenes and non-indigenes. The former are predominantly of the Islamic faith, preferring Koranic to formal education and they are subjected to the feudal rule of the Emir and lesser leaders. The other Nigerians originating mostly from the middle belt and southern parts of Nigeria, with their background of European missionary activities, are mostly Christians. They therefore cherish formal education and so they take full advantage of all the educational establishments in Zaria—over 12 primary schools, three secondary schools, two teacher-training colleges, other vocational and technical training schools, and the Ahmadu Bello University with its student population of over 10 000. The areas of residence of the indigenes and non-indigenes differ to some extent. Although indigenes and non-indigenes are to be found in all areas, the highest concentration of the indigenes is in the old walled City (Fig. 2.4) There, the pace of modernization is very slow when compared to the other Zaria settlements—Tundun Wada, Sabongari and Samaru.

Formal education

During and before the period of this survey, formal education was neither compulsory nor free in Nigeria. However, fees for primary education were so low that most parents could afford to send their children to school if they wanted to, provided there was a school in the area. Primary education, which starts at about the age of 5 years, lasts for 7 years and is followed by secondary education for 5–6 years English, the country's official language, is taught from the primary school level and it is the medium of instruction in all the educational establishments, but vernacular languages are also taught However, many women in this survey whose formal education ceased at primary level were not fluent in written or spoken English.

Cultural features

A striking feature of Hausa life is the extremely low status it accords women. Apart from being semi-secluded, women of child-bearing age scarcely share in decision making, even about child-bearing (Harrison 1983) Most uneducated Hausa girls marry before the menarche (Madauci *et al.* 1968) and so child-bearing often starts well before the girls are fully grown. In addition, there are other traditional customs which influence the results of child-bearing. The first is the gishiri cut, a traditional operation in which the vagina is cut, usually by old women using a razor blade. We have seen it used as treatment for the following conditions: obstructed or prolonged labour, coital difficulties, menstrual and marital problems, infertility, backache, headache, dysuria and even goitre This operation has very serious consequences, such as vesicovaginal fistula, complete division of the urethra, sepsis and even death through haemorrhage. Another custom is 'kunya', which 'prevents a girl from telling anyone about her pregnancy or asking any questions about childbirth' (Trevitt 1973), because young girls having their first babies are expected to be shy or modest about it. For them, in particular, it is traditional to give birth at home and, when they do, the apathy displayed during pregnancy continues thereafter. Under the influence of

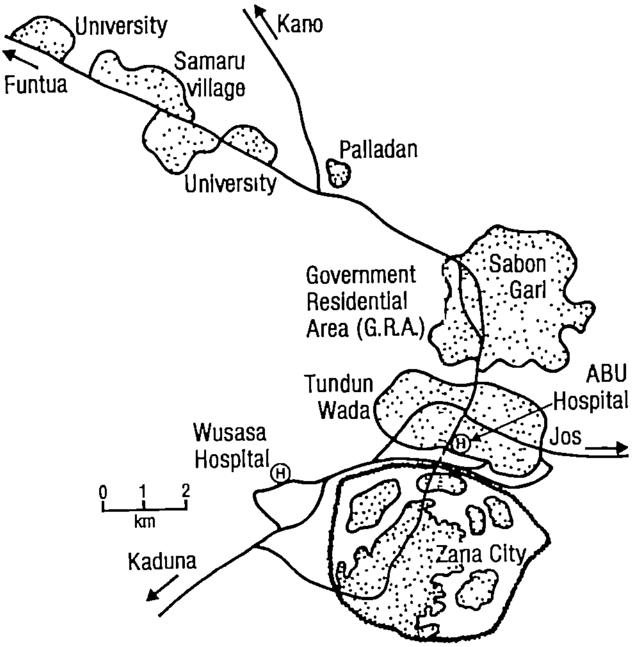

Fig. 2.4 Map of Zaria showing main areas and hospitals Reproduced by kind permission of the editor, from Greenwood *et al.* (1979*a*).

kunya, the natural bonding between mother and child is severed or suppressed. For example, a teenage mother is often reluctant to pick up her first child even when it is crying with hunger As for the mother herself, subsequently recounting her obstetric history, she may unwittingly ignore the actual first pregnancy, referring to her second as her first.

During the puerperium, it is also traditional for women to sleep in overheated rooms (temperature 50°C) and to bath with excessively hot water (temperature up to 80°C) Burns, scalds and peripartal cardiac failure (Davidson & Parry 1978) all result from this practice. Such injuries, especially those on the breasts and buttocks, sometimes become infected and gangrenous, not infrequently leading to septicaemia In common with other Nigerians, Hausa women dislike operative delivery and go to great lengths to avoid caesarean section, which they see as a sign of reproductive failure. Autopsies are not performed for religious reasons.

Originally, the Fulanis were a pastoral people, and some still are. However, intermarriage between the Hausas and Fulanis has occurred on a large scale and nowadays they both share important cultural features, such as religion, language and attitudes towards formal education.

The lifestyle of most of the other Nigerian women is in sharp contrast to that of the Hausa and Fulani. For them, the opportunity to create a better life for themselves is nearly as good as for the men, although restricted to some extent by polygamy.

Maternity services

Antenatal care

During most of the period of this survey, there were only two hospitals which provided maternity services in Zaria (Fig. 2.4) One was a fee-paying mission hospital and the other was ABU Hospital, which was attended by the vast majority, partly because it was free. No referral system was in operation and women who sought maternity care were largely unselected. As their numbers increased (Figs 2.5 and 2.6), so did the pressure on all available resources (Table 2.1).

The basic components of antenatal care in Zaria were in general the same as practised elsewhere, but there were differences brought

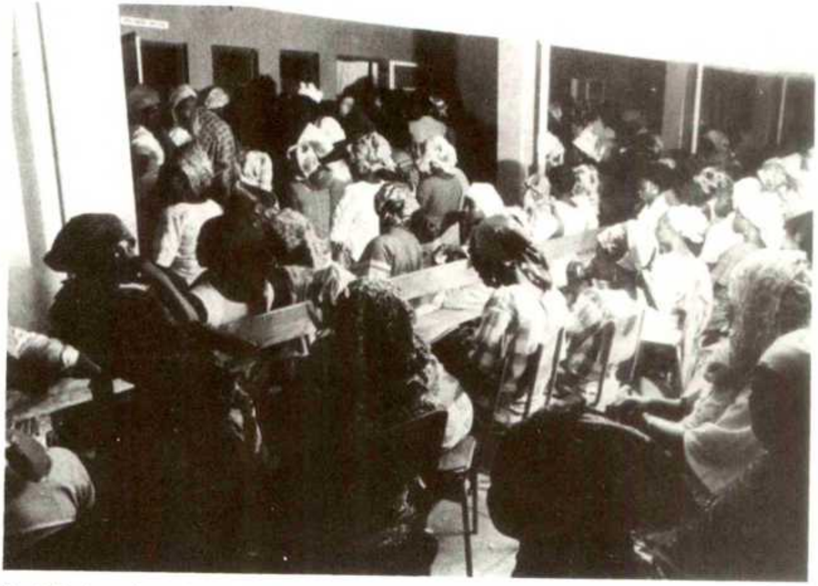

Fig. 2.5. A section of the antenatal clinic in ABU Hospital, Zaria, March 1978; the pregnant patients are in the waiting area adjacent to the examination cubicles.

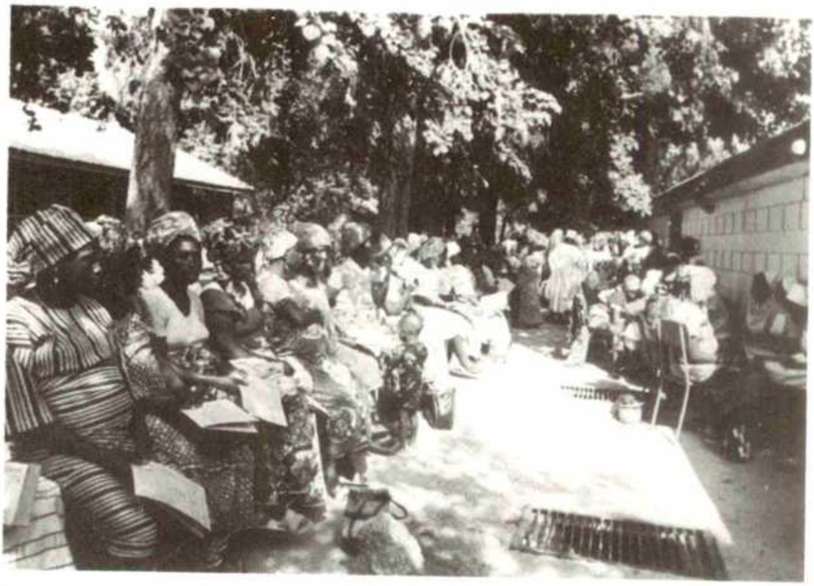

Fig. 2.6. Another section of the antenatal clinic in ABU Hospital, Zaria; March 1978. Right, a group of three student nurses take case histories.

about by the pressure on wards and clinics and by identification of the major obstetric problems. Assessment of uterine size, search for fetal malpresentations and screening for hypertension and proteinuria were part of routine care, but serological tests for syphilis and determination of ABO blood groups, rhesus factor and haemoglobin genotype were carried out only on selected women. Attention was paid to the prevention of anaemia and malaria. For this purpose the drugs that were routinely prescribed were oral chloroquine 600 mg at the first attendance at the antenatal clinic, oral pyrimethamine 25 mg once weekly, ferrous sulphate 200 mg

Table 2.1. Resources and their utilization in the obstetrics and gynaecology department, ABU, Zaria 1970–1977

	1970	1973	1977
Doctors	10	12	22
Trained midwives	—	24	32
Beds (antenatal, postnatal and labour combined)	30	40	54
Operating theatre for all surgical, obstetric and gynaecological cases	1	1	1*
Attendance per antenatal clinic session	150	290	490
Babies born	2168	3971	6585
Caesarean sections	98	285	535
Embryotomies	16	51	62
Forceps and ventouse	105	71	169

Results are numbers
*Twin operating suite

daily, and folic acid 5 mg daily. As far as possible, the haematocrit values of capillary blood samples were determined at the first attendance at the hospital, and sometime in the last 4 weeks of pregnancy.

Another feature of antenatal care was health education which, in Zaria, took only one form. At the start of each antenatal clinic session all attending patients were assembled for a 20-min health talk by a midwife. The topics included simple rules of hygiene, diet in pregnancy, the action of those drugs given to all pregnant women (antimalarials and haematinics), traditional customs surrounding child-bearing, the conduct of labour in the hospital, infant feeding and, most important of all, the significance and risk of prolonged labour. Husbands and other relatives were welcome both at these talks and at the discussions afterwards.

Measurements in the antenatal clinic

Most women did not know their ages or the dates of their last menstrual periods. Therefore, among primigravidae in particular, estimates of maternal ages were made with reference to the age at menarche taken to be 13 years (Marinho *et al.* 1984) Adjustments were then made, firstly for the duration of marriage, secondly for the time intervals from menarche to marriage, and from marriage to the onset of pregnancy. A study of some of these women after they had had their babies showed that under the age of 19 years, there was a good correlation ($r = 0{\cdot}6$) between radiological bone age and clinical estimates of maternal age (C. C. Ekwempu, personal communication, 1983). Gestational ages were largely based on uterine size at the first visit to hospital. Maternal height was measured with the woman standing erect against a vertical metric scale. Such measurements of height were made at the first attendance at the antenatal clinic in the booked women and at admission in labour or after delivery in the women admitted as emergencies. Body weights were recorded to the nearest kg and although all women were weighed at their first antenatal visit, serial weight measurements were only made in women with disease or pre-eclampsia and in the teenage girls described in chapter 5.

Labour ward

In the labour ward (Fig 2.7), as elsewhere in the hospital, there were acute shortages of space, materials and personnel, particularly trained nursing and midwifery staff. During the first half of the period of this survey, there were only nine beds in the actual delivery suite, two in the second-stage room; later the bed complement more than doubled. But working conditions were very austere and all equipment was of the most basic kind. Partograms were used but ultrasonography and other forms of electronic fetal and intrapartum monitoring devices were not available; not that they were missed under the prevailing local conditions.

With an average of 18 deliveries daily and with 10% of the pregnant women arriving in the second stage of labour and 4% in the third stage, there was much overcrowding. Rarely was the daily bed-occupancy rate under 120%. The entire hospital of about 250 beds was served by one operating theatre with two operating tables. All operations whether surgical, obstetric or

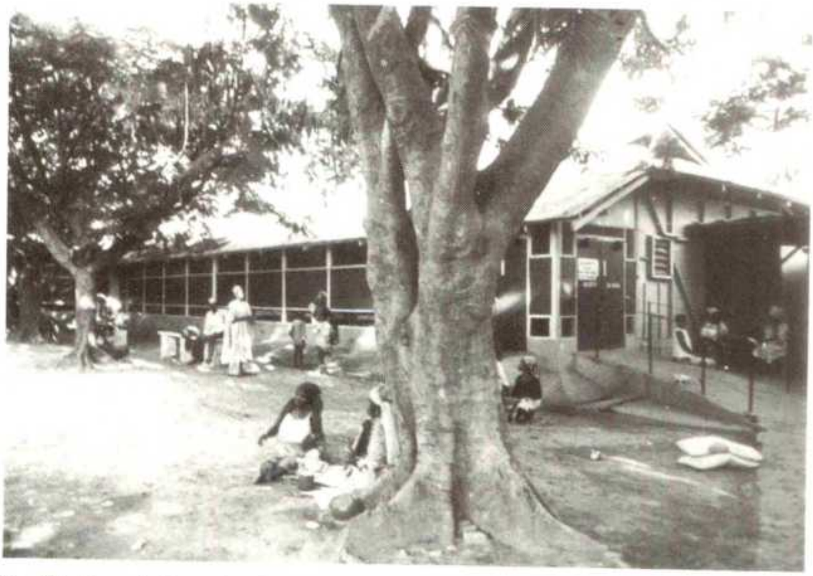

Fig. 2.7. The relatives of patients in labour waiting in front of the labour ward in ABU Hospital, Zaria, March 1978.

gynaecological including operative deliveries took place in it. This arrangement led to further congestion, confusion and overcrowding. The resulting delay in carrying out emergency surgery increased maternal and fetal risks. While supportive laboratory, radiological and blood transfusion services were good, this advantage was partly offset by a shortage of fully trained anaesthetists. Under these conditions, the services rendered by nurse anaesthetists proved quite valuable.

It is reckoned that by 1978 approximately 40% of all deliveries in the Zaria area took place at the ABU Hospital, and that the vast majority of the rest were home deliveries, conducted in accordance with traditional customs (Harrison 1979).

Conditions in the maternity (and lying-in) ward

There was only one all-purpose maternity ward of 33 beds for all pregnant and puerperal patients, no matter how septic they were or how great their need for intensive care. The exceptions were victims of cholera and meningitis treated in the hospital's main isolation unit (Greenwood *et al.* 1979*a,b*; Onyemelukwe *et al.* 1982), others who required specialist medical and surgical care, and finally eclamptics who received intensive care in the labour ward, in a room specifically set aside for the purpose. The maternity ward was always grossly overcrowded and attempts at decongestion failed. Restriction on the number of visitors to the ward was impossible to enforce for cultural reasons. Many defects in the construction of the ward itself could not be rectified, and in their presence, keeping the ward clean and tidy was a major task. Ceiling fans provided the only additional ventilation. In these circumstances, strict barrier nursing was impracticable.

Special care baby unit

This was housed in one room within the maternity ward. In it, work was seriously hampered not so much by shortage of skilled medical manpower but by extreme shortage of trained nurses, and by gross overcrowding. A stage was reached when, in the special care baby unit, the area per baby was only 0·9 m^2 instead of the recommended 2·8 m^2 (Cockburn 1974). Oxygen and four incubators were available, but not ventilators nor monitoring equipment. Expressed breast milk was always available for the tube and bottle fed babies.

Infants

Infant weights were recorded to the nearest 10 g. Live babies were weighed within the first 8 h after birth, while stillbirths, including those delivered by embryotomy, were weighed at delivery. Partly because of the pressure on our resources and party because the women insisted, 70% of all women who had their babies in hospital went home within 24 h, 38% within 12 h. Afterwards, most of them failed to return to the postnatal clinic unless they or their babies were ill, usually with infection. Babies with weights as low as 1·6 kg were sometimes discharged home provided they could suck.

Other services

There were hardly any domiciliary health visiting services. Consequently there was no means of telling the exact number of mothers and babies who died after they were discharged home. Under-reporting of maternal and neonatal deaths was therefore inevitable. The only way to obtain a reasonable estimate of perinatal mortality was to add together all stillbirths and all neonatal deaths (both early and late) which took place in hospital.

Blood donation was voluntary and, except during Ramadan, the supply met the high requirements of 60 units per bed per year. Estimation of blood indices and determination of blood groups and haemoglobin genotypes were by standard techniques (Dacie & Lewis 1975).

Specific records for the maternity survey

During the period of the survey, records of these mothers and their babies were kept on punched cards, adapted from those used in Aberdeen for their extensive epidemiological studies in the 1950s and 1960s. There were 144 coded holes at the margins and additional information was entered in the centre. The information recorded included address, religion, educational attainment, booking status, ethnic group, age, number of total births, number of children alive, abortions, previous caesarean sections, previous vesicovaginal fistula repair, complications of index pregnancy (18 in all), complications in labour (18), mode of delivery (12), complications of puerperium (21) and infant data including birthweight, fetal survival (live birth, stillbirth where intrauterine death occurred before admission to hospital, stillbirth where intrauterine death occurred after admission, early neonatal death or late neonatal death), major or minor congenital malformations, and feeding problems. Dates recorded were those of the last menstrual period, first antenatal attendance, delivery, discharge or death, and puerperal admission. Also recorded were uterine size at booking, blood group, haemoglobin genotype, weight at booking, height, haematocrit values at booking and at delivery, and gestation at delivery. In cases of maternal death, additional items coded were the duration of the patient's stay in hospital before she died and the distance of her home from the hospital and from the nearest main road.

Conduct of the maternity survey

Pilot survey

In October and November 1975, a pilot survey was carried out in which the data on all births in the ABU Hospital were entered on draft pregnancy cards. During this period, all medical and nursing personnel involved in the survey met weekly and reviewed the results. Frequent consultations were also held with members of various departments, in particular paediatrics, medical records and instrument engineering. By December 1975, agreement had been reached on the mode of operation of the actual survey, and on uniformity in the entry of the data on the punched cards.

Actual survey

The survey was conducted without interruption between 1 January 1976 and 30 June 1979, during which time all deliveries in ABU Hospital were recorded, together with information for all those women admitted after they had given birth elsewhere. On discharge of the women from hospital, the consultant in charge used the information recorded in the case notes to fill in the pregnancy card which was subsequently edited usually not later than 1 month after discharge. Both the labour ward delivery register and the register of admissions and discharges in the lying-in ward were used as a check on the accuracy of some of the entries and on the completeness of the records of the actual number of deliveries. The transcription from pregnancy cards to coding sheets began after all 22 774 cards had been compiled.

Computing

Data editing, validation and analysis were carried out at the UK Medical Research

Council's Clinical Research Centre in the Division of Computing and Statistics, where the records were first transferred onto magnetic disc on the Division's DEC 2060 computer system. The resultant data file contained over 5 million characters.

Statistical methods (C E. Rossiter)

The data were examined and modified by forming one-way and multi-way frequency tables. For comparing groups means *t*-test and analysis of variance were used. P-STAT 6.4 (P-STAT Inc. 1981) was employed for data display and description, table formation and hypothesis testing. The statistical package GLIM 3.12 (General Linear Interactive Modelling) (Numerical Algorithms Group 1977) was used for logistic regression. Plots were drawn by calling library subroutines which invoked GINO subroutines (Computer Aided Design Centre 1981) MINITAB 3.0 (Minitab Project 1981) was also used for certain additional analyses.

Primary data

In the 3½ years of this survey, 21 553 women were delivered once and 586 were delivered twice: 49 women died undelivered. Details of the numbers of pregnancies and babies are given in Table 2.2. All but 127 of the 22 188 women were Nigerians. In all 76% were from Zaria itself, a further 20% lived within 50 km and the remaining few travelled up to 180 km, nearly always in labour, to get to the ABU hospital.

Just over 15 000 of the women attended the hospital for antenatal care; most of the remainder had no intention of receiving such care and only attended when complications developed. There were 238 maternal deaths and 2718 perinatal deaths, most of which occurred among those who had not received antenatal care.

During the period of this survey, the total number of births per month rose among the Hausa–Fulanis but not among the other Nigerians. From the first to the last few months of the survey, there was an increase of 150% in the unbooked and a rise of 50% in the booked Hausa–Fulani deliveries (Fig. 2 8).

The major obstetric complications which occurred are shown in Table 2.3 Anaemia, haemorrhage and operative deliveries were common. The latter were often carried out when complications had reached an advanced stage in patients admitted for the first time at the second stage of labour. Under these circumstances, the high requirement for blood transfusion was not surprising

Comments

It is easy to pick on the faults in methodology and data collection employed in this work. In the first place, it could be argued that the use of pregnancy cards was really unnecessary since the data could have been coded directly from information in the case records. However, in our environment, the pregnancy cards on their own served an important additional function. They were invaluable for instructing medical and paramedical personnel, especially students, on how to collect and retrieve data particularly in a rural health setting.

Under the personal record of the women, social class was omitted as information on earnings was difficult to obtain and assessment of

Table 2.2. Number of pregnancies and babies

Births	Number of pregnancies	Number of babies
Singletons	21 958	21 958
Twins	746	1492
Triplets	16	48
Quadruplets	2	8
Conjoined twins	3	6
Total	22 725	23 512
Number who died undelivered	49	—
Grand total	22 774	23 512

Table 2.3. Major obstetric complications in 22 774 pregnancies and 23 512 babies

Group	Complications (number of pregnancies)
Previous operations	Caesarean section: once (787), twice (111), thrice or more (17), repair of previous obstetric fistula (144); salpingectomy for ectopic gestation (43)
Important pregnancy complications	Anaemia (1750), disproportion (1650); prolonged labour (1249); pre-eclampsia (1395), multiple pregnancy twins (746), triplets (16), quadruplet (2). conjoined twins (3), antepartum haemorrhage (780), eclampsia (525); sickle-cell disease (28), hepatitis (12); meningitis (13)
Labour complications	Stage of labour on admission second (2083) and third (911); retained placenta (1086), malpresentations. breech (779), face and brow (62), transverse lie (166); postpartum haemorrhage (649), uterine rupture (203); retained second twin (128), cord prolapse (123); gishiri cut (90)
Mode of delivery (number in parenthesis refer to numbers of babies)	Spontaneous (19 745), caesarean section (2020); breech (746), forceps (538), embryotomies (253), advanced extrauterine pregnancy (4), other deliveries (173)
Puerperal problems	Puerperal hypertension (1812), anaemia (1217), genital and wound sepsis (1058); tubal ligation (346); obstetric fistula—vesicovaginal and/or rectovaginal (79); psychosis (40), acute cervical prolapse (26), tetanus (5), meningitis (6)
Specific procedures treatment and outcome	Blood transfusion (2527); episiotomy (2486), induction of labour medical (345), surgical (297); repair of ruptured uterus (151), hysterectomy (43); maternal deaths (238)
Infant outcome (number in parenthesis refers to numbers of babies)	Discharged home within 24 h of birth (18 378); born before arrival in hospital (2189); birthweight ≤2 50 kg (3739), stillbirths (1762), neonatal deaths (954), congenital defects major (151), minor (131); male/female ratio (1·089)

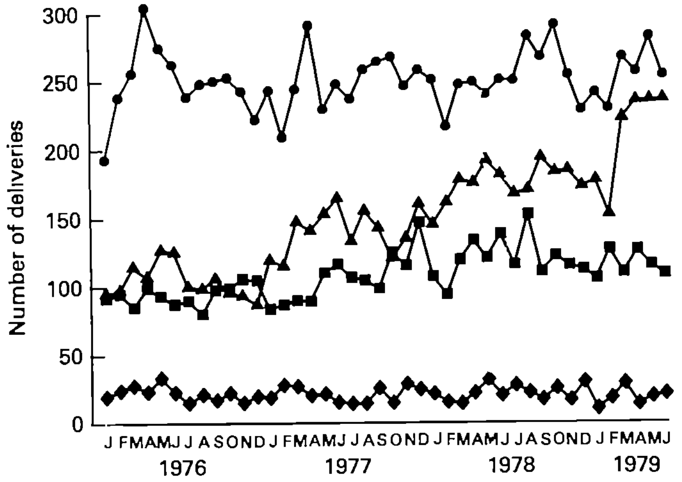

Fig. 2.8. Time trends in numbers of deliveries ■ Hausa-Fulani booked; ▲ Hausa-Fulani emergency; ● other Nigerians booked; ◆ other Nigerians emergency.

social standing was far too problematic in a multi-ethnic society.

Another criticism may be the enormous size of the study. Limiting the work to only a sample of the material and concentrating efforts on obtaining complete data on each individual in that sample would have reduced both the work load and its cost. Instead, the position is that we do not have a complete set of data on every variable. For example, the number of women whose ages were recorded (21 853) is not the same as the number whose parities were stated (22 625) as it should have been if there were no missing data. Therefore women and babies with missing data were often excluded from the analyses, which explains why in this series of reports counts of any particular variable may vary depending on the subject or set of variables under consideration. This problem of missing data notwithstanding, there are other important advantages in the way the information was gathered. The size of the material was such that its collection involved many people for a fairly long time. As the work progressed, most of the participants, including the women themselves, had a better awareness of the obstetric and socioeconomic problems of the area. It was also clear that a better standard of observation and reporting resulted, the effects of which, we are told, are still evident in the area.

Computer packages

The computer packages used were supplied by: P-STAT Inc., PO Box 285, Princeton, New Jersey 08540, USA; Numerical Algorithms Group, 256 Banbury Road, Oxford OX2 7DE, UK; Computer Aided Design Centre, Madingley Road, Cambridge CB3 0HB, UK; and Minitab Project, 215 Pond Laboratory, The Pennsylvania State University, PA 16802, USA.

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3. Antenatal care, formal education and child-bearing

in collaboration with C. E. ROSSITER, H. CHONG, U. G. LISTER, Q. BANO, N. D. BRIGGS, C. C. EKWEMPU & M. T. MEMBERR

Summary. Both formal education and antenatal care had tremendous impact on the results of childbearing. In women who had never had any formal education nor received antenatal care, that is 33% of the survey population, maternal mortality was 29 per 1000 deliveries, perinatal mortality was 258 per 1000 total births and 26% of the babies weighed ≤2·50 kg. With education and antenatal care combined, as was the case in 10% of the survey population, the maternal death rate was 2·5 per 1000 deliveries, perinatal mortality rate was 30 per 1000 total births, and only 8% of the babies were of low birthweight Among women in their thirties and beyond, the average number of previous births per woman in the illiterate group (5·4) was double that in those who had received post-secondary education and child mortality rate at 25% was three times as high. Formal education, by changing social attitudes, holds the key to improvements in maternal and perinatal health.

Antenatal care is known universally to be associated with a marked reduction in maternal and perinatal morbidity and mortality especially under third world conditions (Canon & Hartfield 1964). Yet existing social attitudes often hinder women from using available health care facilities at great cost in both maternal and fetal lives (*Lancet* 1981, 1983) This report strengthens the belief that under these circumstances, formal education (Caldwell 1981) is an important key to better perinatal health.

Groups of women and babies

For the purposes of assessing the influence of antenatal care and formal education on childbearing, all the women and their babies were considered in four groups· educated-booked, uneducated-booked, educated-emergency and uneducated-emergency, depending on whether or not they had booked and received antenatal care and whether or not they had had formal education.

A woman was regarded as having had antenatal care if she booked for such care and afterwards paid a minimum of two antenatal visits, the last no more than 2 weeks before delivery. There were 15 020 such deliveries out of the total 22 725 deliveries.

Those without antenatal care totalled 7654 deliveries, and they were of three subgroups. The first subgroup was made up of 7016 deliveries where the women concerned had no initial intention of receiving any modern system of maternity care. It was only when they or their newborn babies became ill and their own traditional remedies failed to give relief that they reported to hospital. The second subgroup consisted of 424 deliveries and all were defaulters; they had initially attended the ABU hospital for antenatal care and then defaulted for over 8 weeks before reporting again during labour. The 214 deliveries included in the third subgroup comprised women who reported to the ABU hospital in the last fortnight of pregnancy because they were dissatisfied with the care they were getting elsewhere, usually outside Zaria.

Forty-nine women had died undelivered; of these, 46 belonged to the first subgroup of unbooked women and three were booked. The booking status was not known for 51 deliveries.

A woman was regarded as educated if she had received formal education even at primary school level

Biological characteristics and results of child-bearing

In the survey population as a whole, maternal age ranged from 9 to 50 years, parity from 0 to 24 and height from 1·16 to 1·93 m. Table 3.1 shows where the women lived, their religion and ethnic groups in relation to education and booking status. The commonest obstetric problems encountered in the area—contracted pelvis and its sequelae, anaemia, eclampsia and haemorrhage (Appendix 3.1)—were mostly related to poverty, harsh environmental influences and a dearth of, or poor utilization of, health facilities.

The educated-booked women had significantly fewer problems and the uneducated-emergency admissions fared worst on practically every count (Appendices 3.2–3.5 and Table 3 2). Even where medical facilities were freely and equally available to all, as in the case of the Zaria residents, such facilities were better used by the educated women This explains why, among the educated women with cephalopelvic disproportion, labour was seldom obstructed, and why uterine rupture, obstetric fistula and delivery by embryotomy hardly featured in the way they did among the uneducated women.

Two other results are worth highlighting. No educated woman allowed herself to have a gishiri cut, whereas it occurred in 90 of the uneducated. Of the women who had had a previous major operation, such as caesarean section and repair of obstetric fistula, virtually all those who were educated reported for antenatal care, but more than 20% of the uneducated failed to

Table 3.1. Social characteristics by booking status and formal education

Social factor	Educated-booked Number	Educated-booked % of group	Educated-emergency Number	Educated-emergency % of group	Uneducated-booked Number	Uneducated-booked % of group	Uneducated-emergency Number	Uneducated-emergency % of group	Total Number	Total % of group
Residence										
Outside Zaria	65	2·7	7	11·9	939	7·5	4372	57·6	5383	23·9
In Zaria	2312	97·3	52	88·1	11 558	92·5	3218	42 4	17 140	76 1
Religion										
Christian	1834	80·5	42	73·7	5255	44·1	566	7 6	7697	35·5
Islam	443	19·5	15	26·3	6661	55·9	6879	92·4	13 996	64·5
Ethnic group										
Hausa–Fulani	105	4·6	6	10·7	4348	34·9	6678	88·7	11 137	49·9
Other Nigerians	2193	95·4	50	89 3	8094	65·1	853	11·3	11 190	50·1

Table 3.2. Pregnancy outcome by booking status and formal education

Pregnancy outcome	Educated-booked	Uneducated-booked	Educated-emergency	Uneducated-emergency
Operative delivery/100 babies	10·9	10 9	16·9	25 9
Babies with birthweight ≤2·50 kg (%)	7 7	10·8	20·7	29·9
Perinatal deaths/1000 hospital & home births	30	44	169	258
Maternal deaths/1000 deliveries	2·5	1·0	0 0	28·9

For number of women and babies in each group, see Appendices 3.2–3 5 do so. Table 3.3 shows more clearly the influence of antenatal care on fetal outcome and in this analysis, an attempt was made to reduce to the minimum the effects of several biosocial factors, such as height, age, parity, place of residence and ethnic group. Not only was antenatal care associated with a more than three-fold reduction in perinatal mortality, it was particularly effective in reducing fetal loss from stillbirths

Education and the acceptance of antenatal care

Appendix 3.6 and Fig. 3.1 provide a breakdown of the women according to their address, religion, ethnic group and level of education. Of the women in this survey who received formal education, 90% or more also received antenatal care, no matter where they lived or what their religion or ethnic group was. In those without formal education, it was only among the Christians and other Nigerians that as many as 90% had antenatal care.

Only 1% of the Hausa and Fulani women had received formal education compared with 20% of the other Nigerian women.

Education, family size and child survival

Table 3.4, Figs 3 2 and 3.3 show the influence of formal education on the number of previous births and their survival. When compared with women without formal education, those with formal education bore fewer children on average, and they achieved better child survival The level of maternal education was also important: the number of previous total births per woman and the child mortality rate both declined sharply with rising educational attainment. Child survival was at its lowest in early teenage multigravidae.

Discussion

Not all the results presented here are easy to interpret, because the material is all hospital based and so the pattern of distribution of factors such as fetal birthweight, mode of delivery, parity and even maternal age are not representative of the pattern in the population as a whole. Despite this inescapable difficulty, there is no doubt that powerful lessons can be learnt from these results from Zaria

It is worth turning attention first to the women who had neither formal education nor antenatal care. Among them, fetal survival was equally dismal whether their babies were born at home or in hospital (Appendix 3.5, Table 3.5) This interesting finding is not difficult to explain once it is realized that the women in this group never intended to have their babies in hospital in the first instance When, therefore, major complications developed towards the end of pregnancy or in labour, effective treatment was either not given at all (i e. women who continued to remain at their homes), or such treatment was given very late (i.e. women who eventually reached hospital to give birth there). In both groups, many babies were already severely damaged even before birth and so whether they were born

Table 3.3. Fetal outcome by maternal height and booking status in Hausa–Fulani primigravidae aged 20–24 years (singleton births only)

Height (m)	Booking status	Total births (*n*)	Stillbirths (*n*)	Neonatal deaths (*n*)	Fetal loss (% of total births)
≤1·49	Unbooked	23	4	1	21·7
	Booked	15	0	0	0·0
1·50–1·54	Unbooked	66	4	7	16·7
	Booked	30	0	1	3 3
1·55–1 59	Unbooked	50	7	2	18·0
	Booked	52	0	2	3·8
≥1·60	Unbooked	34	2	1	8 8
	Booked	48	1	3	8 3
Total	Unbooked	173	17	11	16·2
	Booked	145	1	6	4·8

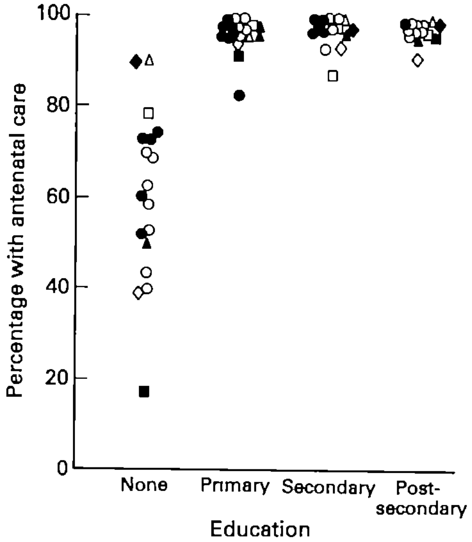

Fig. 3.1. Formal education, biosocial factors and acceptance of antenatal care ○ Age groups, ● parity groups, □ Zaria resident; ■ outside Zaria; △ Christian; ▲ Moslem, ◇ Hausa–Fulani; ◆ Other Nigerians.

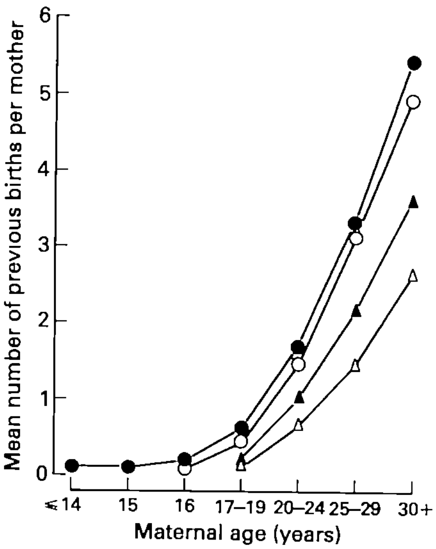

Fig. 3.2. Maternal education and family size ● No formal education, ○ primary education; ▲ secondary education; △ post-secondary education

at home or in hospital hardly made any difference to the prognosis. The plight of the 'uneducated-emergency' group should help to bring into sharp focus the part that traditional birth attendants (TBA) play in maternal and perinatal health care. After all, the uneducated-emergency group of women and the TBA both exist, to a very great extent, in the same environment

Table 3.4. Mean number of previous births and survival by maternal age and formal education

Maternal age (years)	Formal education							
	None		Primary		Secondary		Post-secondary	
	Mean parity	% alive	Mean parity	% alive	Mean parity	% alive	Mean parity	% alive
<15	0·11 (469)	55	0 0 (6)	—	—	—	—	—
15	0.07 (1013)	56	0·0 (19)	—	—	—	—	—
16	0·18 (925)	62	0 08 (40)	33	0·0 (4)	—	—	—
17–19	0·57 (3103)	75	0·42 (234)	82	0 23 (35)	75	0·18 (11)	100
20–24	1·70 (5321)	79	1 47 (519)	87	1·01 (182)	91	0·66 (138)	87
25–29	3·33 (4080)	78	3·18 (408)	89	2 15 (212)	92	1·44 (228)	93
≥30	5·42 (3320)	72	4·95 (149)	87	3·60 (87)	89	2·62 (109)	95

The numbers of women in each group are shown in parentheses

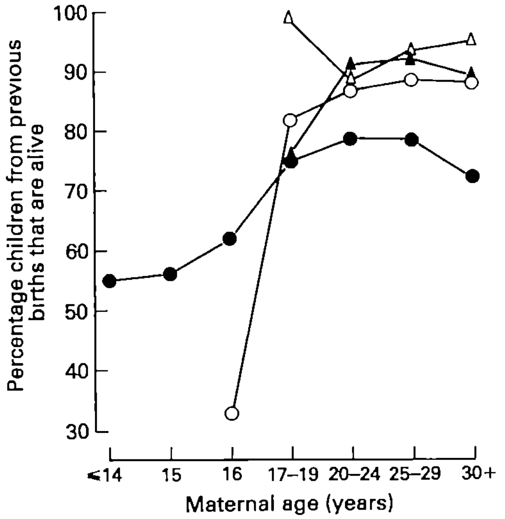

Fig. 3.3. Maternal age, maternal education and child survival rates ● No formal education, ○ primary education; ▲ secondary education, △ post-secondary education.

and the one group serves the needs of the other.

Recognizing that the TBA handle nearly all deliveries in that sort of environment, a strong case has been made for their retraining as a way of reducing the high perinatal mortality rates (Mangay-Maglacas & Pizurki 1981). But in the retraining programmes emphasis continues to be laid more on imparting knowledge of intrapartum skills than on antenatal care. At best, all that can be hoped for is that whenever maternal complications occur during labour, such women will be referred quickly to hospital for expert care, and efforts in this direction have not succeeded in reducing the overall perinatal mortality rate for a variety of reasons (*Lancet* 1983). These results from Zaria indicate that attempts to improve perinatal health should also place considerable emphasis on raising living standards and eradicating mass illiteracy (*Lancet* 1983).

There can be no disputing the fact that both antenatal care and formal education have a tremendous impact on maternal and perinatal health. The issue, however, is complex: in areas such as Nigeria where poverty and illiteracy exist on a large scale, the question may be asked as to whether affluence or formal education holds the real key to better maternal and perinatal health. Real incomes and earnings are very difficult to examine in Nigeria (chapter 2) but elsewhere in Africa and Asia comparisons between nations rather than between different areas within the same country show that infant mortality rates are associated far more with literacy rates than with gross national product. In 47 countries in Africa, the Middle East and Asia, infant mortality rates were between 13 and 190 per 1000 live births, the literacy rates were from 4 to 91%, and the gross domestic product per capita in US dollars ranged between 89 and 6155 (Nortman & Hofstatter 1981). The correlation between infant mortality rates and literacy rates was very highly significant ($r = -0{\cdot}76$, $t = -7{\cdot}84$, d.f. $= 45$, $P \ll 0{\cdot}001$) in contrast to that between infant mortality rate and gross domestic product per capita ($r = -0{\cdot}25$, $P = 0{\cdot}09$). Incidentially there is no significant correlation between literacy rate and gross domestic product per capita ($r = 0{\cdot}11$, $P = 0{\cdot}46$). So, it is hard not to conclude that universal formal education is the more fundamental need and that all the circumstances surrounding the poor maternal and perinatal results reported here are manifestations of the one circumstance.

Table 3.5. Perinatal mortality by booking status formal education and place of birth

	Perinatal deaths/1000 total births			
Place of birth	Educated-booked	Uneducated-booked	Educated-emergency	Uneducated-emergency
Hospital births	29	43	164	258
Home births*	107	85	250	258

For number of total births in each group, see Appendix 3 5.

* Born before arrival at hospital

Support for the idea that formal education rather than per capita economic production has the major impact on birth rate and child survival comes from the Indian State of Kerala (Chopra 1982) In terms of average earnings and average calorie consumption, Kerala is one of the poorest states in India. But then, its literacy rate at 70% is the highest in that subcontinent and both its crude birth rate and infant mortality rate are by far the lowest (Khosla 1979).

The results now being presented once again draw attention to the relation between formal education and family size. They imply that the universal provision of formal education must be a major factor in the reduction of both birth rate and child mortality.

In chapter 2 the point had been made that in traditional Hausa society, firstborn infants of early teenage mothers suffer rejection in a way all subsequent infants never do. Not surprisingly, these children singled out for such harsh treatment in observance of the traditional Kunya custom were the least likely to survive.

Compared to the educated woman, the ill-educated woman in a traditional Northern Nigerian community will almost certainly have had a more deprived childhood with poorer nutrition, will have married while still a child and will have become pregnant while still growing. Her pregnancy, already at greatly increased risk because of that background, will be managed by inadequately trained birth attendants. When serious complications develop, professional help will be sought too late, if at all.

Appendix 3.1. Obstetric complications and previous operations by booking status and formal education

Complication/previous operation	Educated-booked (*n*)	Educated-emergency (*n*)	Uneducated-booked (*n*)	Uneducated-emergency (*n*)
Obstetric complications				
Anaemia	137 (1304)	7 (23)	703 (3325)	1029 (2077)
Disproportion	78	3	495	1066
Prolonged labour	41	2	213	983
Malpresentations	117	4	630	769
Contracted pelvis	43	1	315	739
Pre-eclampsia	215	7	673	483
Multiple pregnancy	60	0	301	404
Eclampsia	10	0	125	389
Postpartum haemorrhage	49	4	206	386
Retained placenta	15	2	169	887
Antepartum haemorrhage				
Placenta praevia	18	1	57	187
Placental abruption	8	2	44	146
Other causes	18	2	83	209
Uterine rupture	3	0	23	177
Previous operations				
Repair of vesicovaginal fistula (VVF)	2	0	74	21
Caesarean section	110	3	550	205
Repair of VVF and caesarean section	3	0	32	12
Total number of pregnancies	2377	59	12398	7590

Numbers of pregnancies where haematocrit values were estimated are shown in parenthesis.

Appendix 3.2. Maternal age, parity and height by booking status and formal education

Maternal characteristics	Educated-booked		Educated-emergency		Uneducated-booked		Uneducated-emergency	
	Number	% of group	Number	% of group	Number	% of group	Number	% of group
Age (years)								
<15	5	0·2	1	1·7	187	1·5	285	4·1
15	19	0·8	0	0·0	446	3·7	569	8·1
16	42	1·8	2	3·5	495	4·1	440	6·3
17–19	270	11·4	13	22·8	2047	16·7	1187	17·0
20–24	831	35·2	18	32·6	3967	32·4	1666	23·8
25–29	848	35·9	16	28·1	3023	24·7	1344	19·2
≥30	346	14·7	7	12·3	2074	16·9	1509	21·6
Total	2361	100·0	57	100·0	12 239	100·0	7000	100·0
Parity								
0	626	26·4	15	25·9	2761	22·3	2887	37·8
1	534	22·5	14	24·1	2418	19·6	975	12·8
2	431	18·1	5	8·6	2198	17·8	860	11·3
3	332	14·0	12	20·7	1759	14·2	655	8·6
≥4	451	19·0	12	20·7	3221	26·1	2250	29·5
Total	2374	100·0	58	100·0	12 357	100·0	7627	100·0
Height (cm)								
≤149	88	3·8	4	8·7	962	8·3	744	18·5
150–154	380	16·3	7	15·2	2823	24·2	1197	29·8
155–159	690	29·7	16	34·8	3748	32·2	1130	28·1
160–164	743	31·9	11	23·9	2883	24·8	723	18·0
≥165	425	18.3	8	17·4	1232	10·5	228	5·6
Total	2326	100·0	46	100·0	11 648	100·0	4022	100·0

Appendix 3.3. Mode of delivery by booking status and formal education (singleton and multiple births combined)

Mode of delivery	Educated-booked		Educated-emergency		Uneducated-booked		Uneducated-emergency	
	Number of babies	% of group	Number of babies	% of group	Number of babies	% of group	Number of babies	% of group
Spontaneous	2169	89·2	49	83·1	11 410	89·1	5895	74·0
Breech	51	2·1	2	3·4	370	2·9	316	4·0
Forceps	47	1·9	1	1·7	209	1·6	276	3·5
Caesarean sections	166	6·8	7	11·9	775	6·1	1090	13·7
Destructive operations	0	0	0	0	21	0·2	231	2·9
Extrauterine pregnancy	0	0	0	0	1	0·0	3	0·0
Others	0	0	0	0	16	0·1	149	1·9
Total	2433	100·0	59	100·0	12 802	100·0	7960	100·0

Appendix 3.4. Fetal birthweight distribution by booking status and formal education (singleton and multiple births combined)

Fetal birthweight (kg)	Educated-booked		Educated-emergency		Uneducated-booked		Uneducated-emergency	
	Number	% of group	Number	% of group	Number	% of group	Number	% of group
≤2·00	55	2 3	8	13 8	408	3 2	911	12·8
2·01–2·50	131	5·4	4	6·9	961	7 6	1213	17 1
2·51–3 00	530	21·8	17	29·3	3658	28 9	2330	32 8
3 01–3·25	466	19 2	10	17 2	2555	20·2	1010	14 2
3·26–3·50	587	24 2	10	17 2	2680	21·2	939	13·2
3·51–4·00	555	22·9	8	13·8	2082	16 5	621	8 7
>4 00	102	4 2	1	1 8	307	2 4	89	1 2
Total	2426	100 0	58	100 0	12 651	100 0	7113	100·0

Appendix 3.5. Fetal outcome by place of birth, booking status and formal education (singleton and multiple births combined)

Place of birth	Outcome	Educated-booked			Educated-emergency			Uneducated-booked			Uneducated-emergency		
		Number	% of group	% of total	Number	% of group	% of total	Number	% of group	% of total	Number	% of group	% of total
Hospital	Live	2339	97·1	96 0	46	83·6	78·0	11 838	95·7	92·5	4646	74 2	58·4
	IUD on admission	15	0·6	0·6	4	7 3	6·8	172	1·4	1·3	896	14·3	11·3
	IUD after admission	25	1·0	1·0	2	3·6	3 4	96	0 8	0·7	231	3 7	2·9
	Early neonatal death	24	1 0	1·0	2	3 6	3 4	241	1·9	1 9	447	7·1	5 6
	Late neonatal death	5	0 2	0·2	1	1 8	1·7	19	0·1	0 1	38	0·6	0·5
At home*	Live	25	89·3	1·0	3	75·0	5 1	398	91·5	3·1	1258	74·2	15 8
	Stillbirths	1	3·6	0·0	0	0 0	0·0	24	5·5	0 2	282	16 6	3·5
	Neonatal deaths	2	7·1	0·1	1	25·0	1·7	13	3·0	0·1	156	9·2	2·0

* Born before arrival at hospital
IUD, Intrauterine death

LIBRARY

Appendix 3.6. Acceptance of antenatal care by formal education and biosocial factors

	Education			
Biosocial factors	Primary *n* (% booked)	Secondary *n* (% booked)	Post-secondary *n* (% booked)	None *n* (% booked)
Residence				
Zaria				
City	86 (93·0)	42 (97·6)	42 (100·0)	2197 (59·2)
Sabon Gari	629 (98·1)	162 (100·0)	30 (96·7)	5231 (87·5)
Tundun Wada	261 (97·7)	107 (97·2)	137 (99·3)	2772 (85·7)
Samaru	298 (96·6)	162 (96·9)	217 (99·1)	2705 (83·0)
Other areas	84 (97·6)	51 (94·1)	58 (96·6)	1906 (55·7)
Outside Zaria				
Funtua	5 (100·0)	1 (100·0)	0	315 (9·5)
Malumfashi	3 (100·0)	1 (100·0)	3 (100·0)	618 (3·7)
Makarfi	1 (100·0)	1 (100·0)	0	231 (16·0)
Others	27 (92·6)	12 (91·7)	12 (83·3)	3629 (19·4)
Religion				
Christian	1075 (97·2)	406 (98·0)	396 (98·7)	5831 (90·1)
Islam	289 (96·9)	100 (96·0)	70 (95·7)	13 575 (49·1)
Ethnic group				
Hausa–Fulani	66 (95·5)	19 (94·7)	26 (92·3)	11 054 (39.3)
Other Nigerians	1329 (97·3)	491 (98·0)	425 (98·6)	8966 (90·3)
Age (years)				
<15	6 (83·3)	0	0	472 (39·6)
15	19 (100·0)	0	0	1018 (43·8)
16	44 (95·0)	4 (100·0)	0	936 (52·9)
17–19	236 (94·5)	36 (100·0)	11 (100·0)	3240 (63·2)
20–24	524 (97·9)	185 (97·3)	141 (97·9)	5627 (70·2)
25–29	416 (98·1)	218 (97·2)	231 (98·7)	4355 (69.1)
≥30	152 (97·4)	92 (97·8)	109 (99·1)	3569 (57·7)
Parity				
0	347 (96·8)	137 (98·5)	155 (98·7)	5447 (52·0)
1	282 (96·5)	122 (97·5)	138 (99·3)	3263 (72·7)
2	237 (98·7)	104 (98·1)	96 (99·0)	2949 (73·0)
3	210 (97·1)	79 (93·7)	52 (98·1)	2323 (74·2)
4+	315 (97·8)	93 (98·9)	51 (96·1)	5187 (60·7)

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1985, Suppl 5, pp 23–31

4. The influence of maternal age and parity on child-bearing with special reference to primigravidae aged 15 years and under

in collaboration with C. E. ROSSITER, H. CHONG, U. G. LISTER, Q. BANO, N. D. BRIGGS, C. C. EKWEMPU & M. T. MEMBERR

Summary. In singleton births, maternal and fetal survival were poorest among primigravidae aged ≤15 years and also in the highly parous women aged ≥30 years. The young teenage girls constituted 6% of the survey population and 30% of the 174 maternal deaths, while the highly parous older women made up 10% of the survey population and 20% of the maternal deaths. The perinatal death rates per 1000 singleton deliveries were 180 for the young teenage girls, 150 for the highly parous groups had under 100 for the others. The major obstetric problems were dystocia due chiefly to contracted pelvis, anaemia, eclampsia, haemorrhage and infections. Emphasis is laid on the fact that the problems of these high-risk groups have their roots in the prevailing social attitudes which universal formal education stands the best chance of changing.

Against a background of poverty and deprivation, traditional customs in Zaria and elsewhere create a situation where child-bearing often starts before the age of 16 years, resulting eventually in a large proportion of women of exceedingly high parity In this chapter, the pregnancy outcomes at various age–parity groups are examined. At the same time, the data were analysed in such a way as to show certain social advantages and disadvantages in the lifestyles of the women in each age–parity group.

Definition of maternal age–parity groups

Based largely on the plot showing the rate of caesarean sections plus the embryotomies at each maternal age from under 13 to over 41 years (Fig. 4.1), the subjects were divided into seven age groups: <15, 15, 16, 17–19, 20–24, 25–29 and ≥30 years As expected, child-bearing before the age of 16 years was not uncommon (Appendix 4.1). Indeed in the 15-year-old group, 76 had already had one previous birth, and three had two previous births. In those reckoned to be aged between 17 and 19, three women had had five previous births.

Maternal age and height

Maternal heights were measured in 80% of the survey population. Among primigravidae, mean heights in the seven age groups were 151·6, 153·6, 155·1, 156·4, 157·6, 158·2 and 157·4 cm respectively.

Maternal education in relation to age and parity

Illiteracy rates were highest among the youngest and among the most parous (Appendix 4.1). Only 0·7% of the 297 women with 10 or more previous births had received any formal education compared with 10 0–13·7% of the women with 0–5 previous births In this respect, the 329 primigravidae aged 25–29 years were at the greatest advantage, 31·9% of them having received formal education.

Family size and child survival

Table 4.1 shows that in all 22 774 pregnancies in the survey population the proportion of women whose parity exceeded 5 was lowest among those with post-secondary education and highest

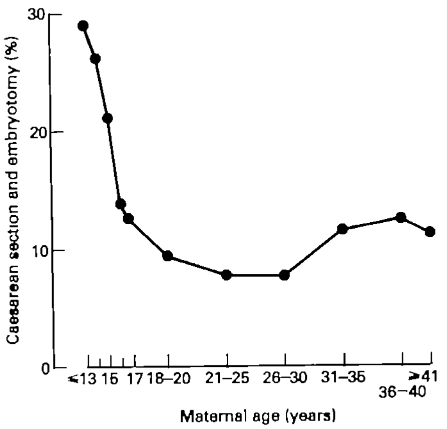

Fig. 4.1. Maternal age, caesarean section and embryotomy rates

among the illiterates: the highest parity in the most educated was 6 rising to 24 in the uneducated group.

Table 4.2 gives some idea of the pattern of child mortality in the Zaria population. A total of 15 156 women already had had at least one previous birth at the time they first reported to hospital for care and only 8739 (58%) had all their children still alive, with this proportion decreasing from 80% in women with only one previous birth to 50% in those with four previous births, and only 6% in women with nine or more previous births. It is particularly striking (Fig. 4.2) that above parity 7, the average number of children alive is virtually constant, implying one birth equals one death thereafter. The most extreme examples of the scale of child mortality were reported by two women, one with 16 previous births but no surviving children, the other with 24 previous births and only five alive.

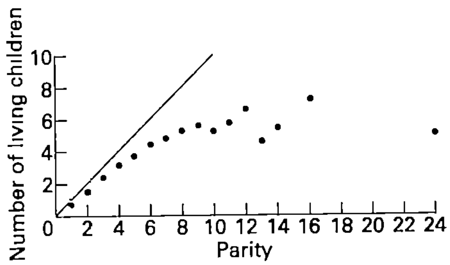

Fig. 4.2. Children alive at each birth number

Pregnancy complications and outcome

Just how dangerous child-bearing is, to both maternal and perinatal health in early teenage girls and in highly parous women aged ≥30 years, can be seen in Tables 4.3 & 4.4, Appendices 4.2–4.4 and in Figs 4.3–4.6. Fig. 4.3 relates maternal age and parity to the prevalence of antenatal complications in all women, irrespective of the booking status. The antenatal complications referred to are anaemia, threatened abortion, pre-eclampsia, hypertension, eclampsia, haemoglobinopathy, antepartum

Table 4.1. Distribution of women by parity and formal education

	Formal education					
Parity	Primary	Secondary	Post-secondary	None	Not stated	Total
0	349	137	156	5661	44	6347
1	284	123	141	3402	38	3988
2	238	106	96	3067	38	3545
3	210	80	54	2421	29	2794
4	145	51	32	1869	14	2111
5	100	27	16	1277	10	1430
6	40	14	4	853	7	918
7	18	2	—	565	4	589
8	10	—	—	399	1	410
9	3	—	—	234	5	242
≥10	2	—	—	290	5	297
Not recorded	—	—	—	99	4	103
Total	1399	540	499	20 137	199	22 774

Table 4.2. Maternal parity and child survival

Parity	Number of women	Children alive: Total number	Children alive: Number/woman
0	6347	0	0
1	3706	3013	0·81
2	3284	5510	1·68
3	2593	6512	2·51
4	1966	6436	3·27
5	1327	5121	3·86
6	860	3842	4·47
7	551	2666	4·84
8	368	1955	5·31
9	221	1258	5·69
10	151	798	5·28
11	68	398	5·85
12	40	263	6·57
13	8	36	4·50
14	8	42	5·25
16	4	29	7·25
24	1	5	5·00
Total	21 503	37 884	1·76

Table 4.3. Maternal death rate per 1000 by age, parity and booking status (singleton births only)

Maternal age (years)	All deliveries			Primigravidae			Parity ≥5		
	Booked	Unbooked	Total	Booked	Unbooked	Total	Booked	Unbooked	Total
<15	5	42	27	5	43	28	—	—	—
15	0	58	31	0	59	33	—	—	—
16	0	18	8	0	19	9	—	—	—
17–19	1	21	7	0	19	7	0	0	0
20–24	1	14	4	1	10	4	0	12	5
25–29	1	18	5	0	9	3	2	23	10
≥30	2	28	11	0	0	0	2	35	16
All ages	1	24	8	1	27	12	2	30	13
No of maternal deaths	13	161	174	2	70	72	4	42	46
No of women	14 396	6693	21089	3448	2569	6017	2048	1393	3441

(Maternal death rate/1000)

haemorrhage, and associated medical and surgical conditions.

Figs 4.4 and 4.5 show the relations between maternal and perinatal mortality, age and parity among singleton births only. Maternal mortality is highest for the very young and for the older highly parous women. The pattern for perinatal mortality is similar except that the rate is raised for the oldest women irrespective of parity. Table 4.3 shows that among all singleton births

Table 4.4. Perinatal mortality rate per 1000 by age, parity and booking status (singleton births only)

Maternal age (years)	Perinatal mortality rate/1000								
	All deliveries			Primigravidae			Parity ≥5		
	Booked	Unbooked	Total	Booked	Unbooked	Total	Booked	Unbooked	Total
<15	74	251	180	75	254	182	—	—	—
15	58	267	171	57	276	179	—	—	—
16	43	219	122	44	226	125	—	—	—
17–19	39	210	96	48	218	112	0*	1000*	333*
20–24	27	205	71	35	179	85	61	271	151
25–29	30	231	80	53	205	106	26	314	134
≥30	42	309	141	174	213	194	36	323	155
All ages	34	240	99	48	226	124	35	317	149
No of perinatal deaths	495	1594	2089	167	581	748	71	441	512
No of births	14 381	6629	21 010	3448	2566	6014	2048	1393	3441

*Based on ≤3 births.

antenatal care was associated with a reduction in maternal mortality rate in all age–parity groups. Its influence on perinatal mortality was just as favourable (Table 4.4). Unfortunately, fetal outcome was not known for 79 births.

Living standards were lowest in the two high-risk groups and so was the proportion of women in this series who reported to hospital for antenatal care (Appendix 4.2). These environmental influences were reflected in the pattern of obstetric complications (Appendix 4.3) and of complicated deliveries (Appendix 4.4).

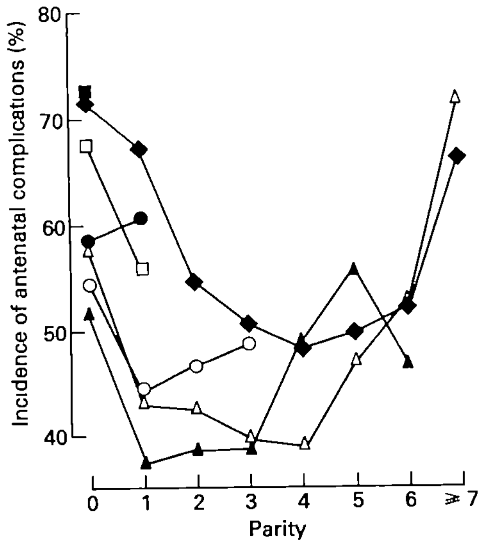

Fig. 4.3 Maternal age, parity and incidence of antenatal complications. Ages: ■ <15; □ 15; ● 16; ○ 17–19; ▲ 20–24; △ 25–29; ◆ ≥30.

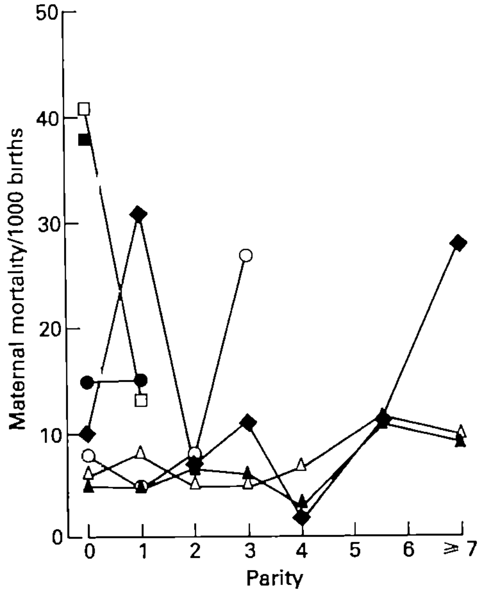

Fig. 4.4 Maternal age, parity and maternal mortality. Symbols as in Fig 4.3.

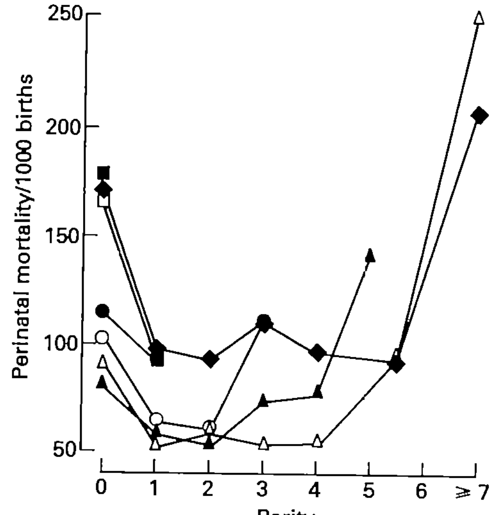

Fig. 4.5. Maternal age, parity and perinatal mortality. Symbols as in Fig 4 3.

Early teenage primigravidae

The majority of the early teenage primigravidae were Hausa–Fulanis (86%) and over 98% were illiterate. They were also more commonly of the Islamic faith (90%) and living in the poor rural environment outside Zaria where health care services were very inadequate even by local standards. Among primigravidae, the proportion who attended hospital was lowest in the very young and they had a higher prevalence of anaemia and eclampsia. In anaemia in pregnancy, the worst forms occurred most often in the youngest girls. Among primigravidae, anaemia (maternal haematocrit <0·30) was found in 189 girls aged ≤15 years, 74 aged 16 years, and from only eight in the oldest age groups to 203 in those aged 17–19 years. However, among those who were anaemic, the proportion with haematocrit <0·19 was 25% in girls aged ≤16 years compared with 0–19% in the older age groups.

In the survey population there were 525 eclamptics, 1650 women with disproportion and 1249 with prolonged labour; 40% of the eclamptics, 20% of those with disproportion and 18% of those with prolonged labour were aged <15 years. In no other age–parity group were the prevalences of disproportion and eclampsia as high as they were in the youngest teenagers Only in the older primigravidae did the frequency of prolonged labour (25·8%) exceed the frequency in the youngest teenagers

Another problem associated with the early teenagers (≤15 years) was the fact that during labour their arrival at hospital was very often unduly delayed. Some 19% of them arrived in the second or third stage of labour compared with 14% in the 16-year-old group and 9–11% in the remaining age groups. Not surprisingly, complicated deliveries were more frequent and radical procedures such as caesarean section and embryotomy had to be resorted to frequently (Appendix 4.4). A total of 90 women had had a gishiri cut, 28 of them were primigravidae, all were <25 years, and 10 were aged <15 years.

There were 191 craniotomies among the 22 725 deliveries; 48 occurred among the 1437 youngest primigravid singleton births in hospital, and there were associated problems. Among the young admitted in obstructed labour due to cephalopelvic disproportion, the pelvis

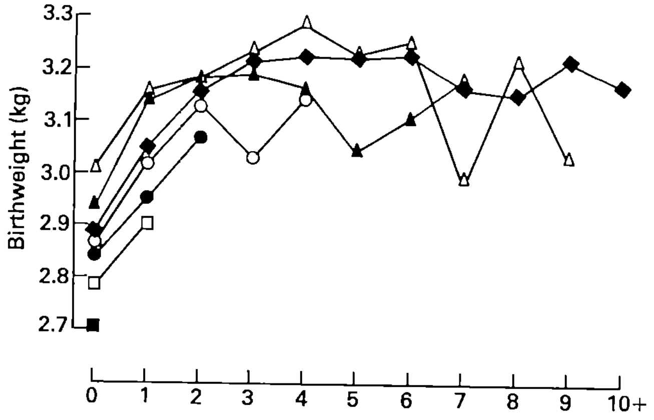

Fig. 4.6. Maternal age, parity and mean fetal birthweight in singleton births. Symbols as in Fig. 4 3.

was often extremely contracted to a degree very rarely seen in older women. For this reason, craniotomy was technically more difficult to perform in early teenage primigravidae. Indeed, in early teenage girls for whom craniotomy had to be performed by K. A H., the degree of disproportion encountered in the course of six of the operations was much greater than was initially anticipated. In all six there was not too much difficulty in perforating the fetal skull, yet the collapsed skull was still too large to permit easy fetal extraction. The immunity of early teenage primigravidae to uterine rupture even in the face of such traumatic delivery is well known, and confirmed in this study.

Of the primigravidae, none aged ≥25 years developed an obstetric fistula (VVF). However, of the 79 women in the whole series who did develop a fistula, 21 were aged ≤15 years and a further eight were aged 16 Their maternal mortality rate (30/1000) was far higher than in any other group and bacterial infection, eclampsia and anaemia were the leading causes.

The threat to fetal survival was even greater than the risk to maternal health: 30% of the babies weighed ≤2·5 kg compared with 7–25% in the other groups. Fig. 4.6 shows that average fetal birthweight was lowest not only for the first and second births, but also especially in the younger mothers. Nearly one in five of their babies died in the perinatal period. The details for the primigravidae who had hospital deliveries were as follows: at the ages of <15, 15, 16, 17–19, 20–24, 25–29 and ≥30 years, the numbers of stillbirths per 1000 total singleton births were 109, 97, 59, 54, 51, 66 and 114 respectively, and the numbers of neonatal deaths per 1000 live births were 86, 84, 64, 56, 34, 29 and 69 respectively

High parity

Women with five or more previous children, particularly those aged ≥30 years, formed the other high-risk group In their case, obstetric haemorrhage featured prominently (Appendix 4.3). Their socioeconomic background was poor as judged by the differences in the literacy rates (Appendix 4.1) and by the increase in antenatal complications (Fig. 4.3) Maternal mortality at over 16 per 1000 was particularly high. The principal causes were bacterial infections, haemorrhage and uterine rupture. However, it was the scale of fetal loss which was quite astounding, with one perinatal death for every seven deliveries. Four in five of these were stillbirths, a higher proportion than for any other age–parity group. The statistics for those aged ≥30 years were as follows· for the singleton births in hospital, the numbers of stillbirths per 1000 total births for parity 1, 2, 3, 4, 5–6, 7–9 and ≥10 were 65, 79, 70, 76, 68, 158 and 210 respectively; the numbers of neonatal deaths per 1000 live births were 36, 13, 47, 23, 29, 49 and 56 respectively.

Discussion

In part, these results confirm what is already known about the influence of maternal age and parity on the results of child-bearing. The risks of high parity are very evident and the fact that child-bearing is least hazardous in women aged 20–29 years in the second, third and fourth pregnancy is also very apparent. Clearly, under Northern Nigerian conditions, whatever biological advantage women in their twenties have, there are other factors related to their social attitudes which protect them against unfavourable pregnancy outcome. Their superiority over all groups of older women and some primigravidae aged ≥20 years was not because they were taller but because a larger proportion of them had had formal education, with all that this implies, as discussed in chapter 3.

The main interest in this report must centre on the fate of the early teenagers (aged ≤15 years). They constituted nearly 6% of the survey population and 30% of all maternal deaths among singleton pregnancies, a fate not even surpassed by those of high parity (≥5 and aged ≥30 years) who made up 10% of the population and 20% of maternal deaths. Russell (1982) and many others have reported on pregnancy outcome in girls aged <16 years (Scher & Utian 1970; Efiong & Banjoko 1975), and in most such reports, especially those from affluent societies (Duenhoelter *et al.* 1975; Dott & Fort 1976; Bremberg 1977; Sandstrom 1977), the conclusions drawn are that although, at that age, growth especially of the bony pelvis is incomplete (Moerman 1982), child-bearing is only marginally more risky than it is in older women. In such societies, the efforts that are being made to tackle the problems of early teenage pregnancy concentrate on giving social and psychological support, on providing sex education, birth control and pregnancy termination, the aim being to ensure that formal education is not unduly interrupted.

The situation in Northern Nigeria is very different To begin with, neither stigma nor favour is attached to early teenage pregnancy. Such girls are the most deprived, with over 98% of those who attended hospital being illiterate and with 60% of them being unbooked emergency admissions. By custom among the Hausas and Fulanis, there is a strongly held belief that home delivery is best for all primigravidae, particularly if they are very young. Judging from the trends in maternal height reported here, there is no doubt that, at the age of 16 years, skeletal growth is far from complete. Moerman (1982) has shown that at this age the bony pelvis is even less mature than the maternal height would suggest, which explains why dystocia is so frequent, the high incidence of low-birthweight babies notwithstanding.

There is the possibility that, apart from the bony pelvis, other pelvic organs may also be immature in early teenage primigravidae. The frequency of complications associated with pregnancy terminations in early teenage girls and in older women was compared by Cates *et al.* (1983) and by Schultz *et al.* (1983) from the United States. Fever, haemorrhage, sepsis, uterine perforation and the need for both blood transfusion and major surgery were all encountered less often in early teenage girls than in older women. However, the younger girls aged ≤17 years were much more liable to cervical injury during dilatation of the cervix and suction curettage.

Eclampsia was another major obstetric problem in these very young girls. Antenatal care is not always successful in preventing it, because the disease is often rapid in onset especially when labour is prolonged or obstructed as so often occurs among these girls. Then, there are the problems of infection and poor nutrition. Zaria is an area holoendemic for malaria There, early teenage primigravidae (Fleming *et al.* 1984) are much more susceptible to the disease than older and parous women, and malaria is the principal cause of pregnancy anaemia, with deficiency of iron and folic acid also playing some part. So the increased frequency of pregnacy anaemia among early teenage primigravidae merely reflects the fact that a large proportion of them have not received the routine antenatal protection against malaria, and that their nutritional needs are not being adequately met It must be concluded that the exceedingly high mortality and morbidity rates in these girls have resulted from the combination of physical immaturity, severe deprivation and frequent infection.

The death and destruction which await early teenage primigravidae is not confined to hospital births only. Of 1443 patients with vesicovaginal fistula reported by Tahzib (1983) from Zaria, over 60% occurred following home delivery and one in three was aged ≤16 years. Furthermore, the younger patients had the more severe lesions. However, the hazards are not just physical. During their incontinence, the girls are ostracized (Murphy 1981), but even after they are made continent by surgery, some remain permanently damaged both physically and psychologically by the experience.

Obviously, the provision and utilization of health care facilities will help towards saving maternal and fetal lives, particularly among the early teenage primigravidae. However, in their case, the source of their plight is deeply rooted in traditional customs and beliefs. So, unless social attitudes change, the chances are that efforts being made to improve the results of child-bearing will meet with only limited success, a point strongly stressed in an earlier Zaria study (Harrison 1981).

Appendix 4.1. Proportion of women with formal education by age and parity

	Maternal age (years)								
Parity	<15	15	16	17–19	20–24	25–29	≥30	Not recorded	Total
0	1·3% (473)	2 0% (964)	5·0% (826)	9 5% (1992)	18·2% (1450)	31·9% (329)	15·2% (99)	0·9% (214)	10 1% (6347)
1	0 0% (7)	0 0% (76)	2·2% (135)	7·1% (1105)	14·8% (1782)	27·6% (615)	21·4% (131)	4·4% (137)	13 7% (3988)
2	0·0% (1)	0 0% (3)	0·0% (20)	3·4% (356)	12·0% (1745)	17·2% (999)	14 3% (301)	2·5% (120)	12·4% (3545)
3	—	—	0·0% (2)	4 1% (74)	9·1% (962)	15 6% (1214)	13 6% (448)	3·2% (94)	12 3% (2794)
4	—	—	—	0 0% (11)	4·1% (387)	13·5% (996)	11 7% (642)	4·0% (75)	10·8% (2111)
5	—	—	—	0 0% (3)	4 2% (142)	11·9% (586)	10·5% (638)	0 0% (61)	10·0% (1430)
6	—	—	—	—	7 0% (43)	6·4% (295)	6·9% (523)	0·0% (57)	6·3% (918)
7	—	—	—	0·0% (1)	0·0% (14)	4·0% (126)	3·3% (418)	3·3% (30)	3·4% (589)
8	—	—	—	—	0·0% (5)	1·6% (61)	2·9% (310)	0·0% (34)	2·4% (410)
9	—	—	—	—	0 0% (1)	0·0% (30)	1 5% (195)	0·0% (16)	1·2% (242)
≥10	—	—	—	—	0 0% (3)	0·0% (23)	0·8% (256)	0·0% (15)	0·7% (297)
Not recorded	—	—	0·0% (1)	0·0% (9)	0·0% (23)	0·0% (22)	0·0% (26)	0·0% (22)	0·0% (103)
Total	1·2% (481)	1·8% (1043)	4·5% (984)	8·0% (3551)	13·0% (6557)	16·3% (5296)	8 9% (3987)	2·1% (875)	10·7% (22 774)

Total number in each group is shown in parenthesis.

Appendix 4.2. Social factors by age and parity (singleton births)

	Primigravidae age-groups (years)							Multigravidae age-groups (years)	
Social factors	<15	15	16	17–19	20–24	25–29	≥30	20–29 (para 1–4)	≥30 (para ≥5)
Number of women	466	940	814	1961	1420	320	93	8366	2210
Residence									
Zaria									
City	16·1	13·8	11·7	11·0	7·3	6·9	12·9	9·3	11·0
Sabongari	12·4	15 5	21·7	26·2	25·4	17·8	8·6	32·8	26·9
Tundun Wada	11·6	14·5	15·0	15·0	15 1	20·3	9·7	16·1	11·2
Samaru	7·7	8·4	13·6	15·3	18 3	19·4	16·1	17 7	10 9
Other areas	6·9	8·6	9·0	9·8	8·5	8·4	14·0	9·4	9 4
Outside Zaria	45·3	39·1	29·0	22 7	25·5	27·2	38·7	14 8	30·6
Hausa–Fulani	90·1	83·4	67·1	50·1	41·9	45·9	72·0	34·7	57·2
Unbooked	60·1	55·5	44·6	37·9	35·1	35·0	50·5	20·8	42·2
Islamic religion	91·8	87·7	74·4	62·2	54·7	52·8	77·4	51·0	70·5

Results are percentages

Appendix 4.3. Obstetric complications by age and parity (singleton births)

	Primigravidae age-groups (years)							Multigravidae age-groups (years)	
Complication	<15	15	16	17–19	20–24	25–29	≥30	20–29 (para 1–4)	≥30 (para ≥5)
Number of women	466	940	814	1961	1420	320	93	8366	2210
Anaemia	15·5	11·5	8·7	10·1	8·3	6·3	7·5	6·0	7·4
Pre-eclampsia	11·6	10·4	10·3	10·2	9·9	15·0	12·9	3·4	5·8
Eclampsia	16·7	12·8	7·4	4·9	2·7	2·5	3·2	0·5	0·3
Antepartum haemorrhage	1·5	1·3	0·9	0·7	1·3	1·6	1·1	1·8	5·4
Disproportion	27·3	22·1	13·3	9·5	8·7	10·9	16·1	4·1	7·1
Labour >24h	17·2	14·9	11·3	7·9	7·5	9·4	25·8	2·2	6·1
Retained placenta	8·6	7·7	6·4	4·4	5·6	4·7	4·3	3·0	6·1
Postpartum haemorrhage	3·2	2·6	3·3	2·3	2·7	2·5	1·1	2·0	4·5
Uterine rupture	0·0	0·2	0·0	0·1	0·1	0·0	0·0	0·7	2·7
VVF/RVF	1·7	1·3	1·0	0·3	0·5	0·0	0·0	0·1	0·5
Congenital abnormalities									
Minor	1·3	0·7	0·5	0·5	0·4	0·9	0·0	0·4	0·6
Major	0·4	0·4	0·6	0·5	0·6	0·3	0·0	0·5	1·1

Results are percentages

VVF, Vesicovaginal fistula; RVF, rectovaginal fistula

Appendix 4.4 Mode of delivery by age and parity (singleton births in hospital)

	Primigravidae age-groups (years)							Multigravidae age-groups (years)	
Mode of delivery	<15	15	16	17–19	20–24	25–29	≥30	20–29 (para 1–4)	≥30 (para ≥5)
Number of births	413	845	743	1824	1312	302	89	7811	1971
Spontaneous	57·9	65·1	75·2	81·1	81·4	73·2	50·6	90·0	81·5
Vaginal breech	1·9	1·8	1·9	1·9	1·8	1·7	2·2	1·6	3·1
Forceps	9·4	8·5	7·3	5·4	5·9	6·6	13·5	0·7	1·0
Caesarean	26·2	20·2	12·8	10·1	10·1	17·2	30·3	6·6	10·7
Embryotomy	4·4	3·9	2·8	1·3	0·8	1·0	1·1	0·5	1·5
Extrauterine	0·0	0·0	0·0	0·0	0·0	0·0	2·2	0·0	0·0
Other	0·2	0·5	0·0	0·1	0·0	0·3	0·0	0·6	2·3

Results are percentages.

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5. Growth during pregnancy in Nigerian teenage primigravidae

in collaboration with A. F. FLEMING, N. D. BRIGGS & C. E. ROSSITER

Summary. Sixty-nine primigravidae, 59 of them aged between 13 and 16 years, were placed on various combinations of antimalarial drugs, folic acid and iron throughout the second half of pregnancy and the puerperium. Between their first attendance at the antenatal clinic and 1–60 days after delivery, more than half of these pregnant teenage girls increased in height by 2–16 cm. Haematinic supplementation and growth of both the fetus and the mother were found to be linked. When compared with girls who did not receive nutritional supplements, a significantly greater proportion of girls who were supplemented grew by ≥2 cm during pregnancy and showed a significant correlation between increase in height and mean weekly weight gain. This growth during pregnancy was highly related to the haematocrit level at the 28th week of pregnancy, after an average of 10 weeks' treatment. Fetal birthweight was correlated with serum folate activity at the 36th week of pregnancy. Because young teenage girls continue to grow during pregnancy, when determining the relation between their heights and reproductive performance, calculations must be based on heights taken towards the end rather than at the beginning of pregnancy.

Wherever it is traditional for girls to marry early, child-bearing often starts in the early teenage period. Partly because of the adverse socio-economic circumstances under which the majority of such girls live and partly because of their inherent biological characteristics, they give birth to small babies (Rehan & Tafida 1979; Russell 1982), their perinatal mortality is high, and when compared with women in their early twenties, the risk of pre-eclampsia and eclampsia is greatly increased, as is the incidence of pelvic contraction (chapter 4). In areas poorly served by health services, obstructed labour and obstetric fistulas frequently result (Murphy 1981; Murphy & Baba Tukur 1981). In West Africa, the same teenage primigravidae are very prone to become anaemic, due to a combination of malaria and deficiencies of iron and folate (Fleming *et al.* 1984). Under these circumstances, if a young pregnant girl, who is still growing, is made to compete with the fetus for nutrients, it is not known whether or not maternal growth continues or falters during pregnancy. Even if such young pregnant teenagers grow, the extent to which malaria and deficiencies of iron and folate affect their height and growth rate during pregnancy is unknown. To investigate these problems, 228 selected Hausa primigravidae were placed on five different combinations of malarial chemoprophylaxis, iron and folic acid supplements and the course and outcome of their pregnancies were studied by measurements of heights and blood folate levels both in pregnancy and in the puerperium. Here attention is being focused not on pregnancy anaemia but on the finding that under certain conditions, the heights of teenage primigravidae continue to increase during pregnancy.

Patients and methods

All except two of the 228 girls were married, the pregnancies being wanted in all cases. All were in good physical condition, and they were reckoned to be 8 to 24 weeks pregnant when they first attended the antenatal clinic. Girls with sickle-cell disease or other haemoglobinopathies were excluded at this stage. Antenatal care, conducted in a routine manner with the assistance of research midwives, was held in a special clinic. Maternal heights were measured twice, at first attendance at the antenatal clinic and 1–60 days after delivery. All measurements were made to the nearest cm, with the subjects standing erect against the same vertical metric scale Apart from haemoglobin electrophoresis, the other investigations carried out serially during pregnancy and in the puerperium included haematological indices, serum and red cell folate levels using *Lactobacillus casei*, assay of serum vitamin B12 using *L. leishmanii* (Fleming *et al.* 1984) and a search for malarial parasitaemia.

Allocation of the patients to the five treatment groups, A to E, was by randomization and the medication was double-blind, the identity of the tablets not being known to the researchers before the analysis of the data. Group A had placebos only, all the rest including group B had a single dose of chloroquine (600 mg base) once, followed by daily oral proguanil (100 mg). In addition, group C had iron (60 mg per day) as ferrous sulphate, group D had folic acid orally (1 mg daily) and group E had both iron and folic acid in the above dosages. Informed consent for this work was obtained from the girls and their husbands or guardians.

Data from the following were excluded from the analysis: 66 for non-compliance with drug therapy, 29 for defaulting even before delivery; 18 developed serious complications and were withdrawn from the trial because their lives would have been in danger if antimalarial and other supplements had continued to be withheld; six for abortion; one for multiple pregnancy; one for mental subnormality; and 38 because their heights were not recorded in the puerperium, although in all other ways they were treated exactly like those who remained in the study Thus, 69 were left for analysis; one was a light cigarette smoker

Non-compliance was common and easy to detect in these cases. When the girls were seen in the antenatal clinic and told to report back after a specified number of days or weeks, the supply of tablets they took home with them was only sufficient to last until the day of their next scheduled visit to the antenatal clinic. Failure to keep to an appointment meant that during the period of temporary default, often lasting 2–3 weeks, the supply of tablets ran out and none was taken. One consequence of their default was that some who were supposed to be protected against malaria, were not. These criteria for rejection, particularly in terms of non-compliance, are much stricter than are usually applied in more developed countries, but failure to remove this group of 66 girls could have obscured any positive findings on the effects of supplementation of diet.

At the end of the trial, all those who were aged ≥17 years in all five groups were constituted into a sixth group, the late teenagers, among whom three had placebos only, four had antimalarials only, one had antimalarials combined with folic acid and two had malaria chemoprophylaxis with added iron and folic acid supplements. The girls still remaining in groups A to E were all aged between 13 and 16.

Statistical methods

To compare continuous variables such as height, Student's *t*-test was used without transformation of any variable. The log likelihood ratio test was used to compare counts, such as the number of girls who grew >2 cm.

Results

Antimalarial, folic acid and iron supplementation effects

In the groups of teenagers studied the mean age, the mean initial height and weight and the average durations of observations were all comparable (Table 5·1) The striking differences were to be found in the changes in maternal heights and weight gain per week with the girls receiving iron or folic acid or both growing much more than those receiving neither.

Haematological results

The mean haematocrit values in the five groups of early teenage girls varied between 0·35 (SD 0·06) and 0·37 (SD 0·04) at the beginning of pregnancy, and between 0·34 (SD 0·05) and 0·37 (SD 0·04) at the end of pregnancy. Two girls were anaemic (haematocrit ≤0·29) at booking and a third became anaemic by the 28th week of pregnancy, one further became so in the puerperium, due to a combination of iron deficiency and *Plasmodium falciparum* malaria.

Table 5.2 shows the changes in blood folate activities during pregnancy and in the puer-

Table 5.1. Characteristics of teenage Nigerian primigravidae

Characteristic	Late teenagers	Treatment groups of early teenagers: A	B	C	D	E
Number of girls	10	10	18	12	10	9
At booking						
Age (years)	18·2 (1·9)	14·8 (0·8)	14·9 (0·7)	15·2 (0·8)	15·2 (0·9)	15·2 (0·4)
Height (cm)	153·9 (7·9)	156·8 (3·6)	155·8 (5·5)	152·9 (6·4)	154·1 (6·0)	155·9 (4·3)
Weight (kg)	50·6 (4·1)	49·1 (8·7)	49·8 (4·4)	47·5 (4·5)	48·0 (5·1)	49·8 (5·2)
Changes during pregnancy						
Increase in height (cm)	1·2 (1·7)	1·1 (1·3)	1·1 (1·2)	3·3 (4·5)	3·0 (2·6)	2·1 (1·3)
Proportion with increase in height of ≥2 cm	30%	30%	28%	67%	80%	67%
Weekly weight gain between first & last antenatal attendance (g)	310 (91)	300 (204)	295 (130)	379 (183)	348 (147)	363 (137)
Interval between measurements (days)						
First antenatal visit–delivery	149 (25)	156 (37)	152 (25)	144 (32)	156 (19)	149 (36)
First antenatal visit–first postnatal visit	188 (36)	192 (38)	198 (28)	186 (29)	200 (29)	208 (38)

Results are means (SD).

Treatment group A, Placebo, B, antimalarials only, C, antimalarials + iron, D, antimalarials + folic acid, E, antimalarials + folic acid + iron.

Table 5.2. Blood folate activity during pregnancy and in the puerperium in early teenage primigravidae

	Treatment group						
	No folic acid supplements			Folic acid supplements			Significance of difference
Period of examination	Mean	SD	No	Mean	SD	No	*P*
Red cell folate (μg/l)							
At booking	337	206	40	413	135	19	0·15
28 weeks gestation	302	217	37	460	249	14	0·03
36 weeks gestation	230	142	30	339	207	15	0·04
Labour	240	169	14	396	260	10	0·09
Puerperium	214	127	36	232	138	16	0·64
Serum folate (μg/l)							
At booking	9·2	4·5	40	11·4	6·1	19	0·13
28 weeks gestation	8·9	5·5	37	18·3	6·6	15	0·000004
36 weeks gestation	7·2	4·8	31	14·1	6·4	15	0·0002
Labour	8·7	6·9	15	14·4	7·6	12	0·05
Puerperium	7·8	6·9	37	8·9	6·1	16	0·59

perium. The mean serum and red cell folate levels were higher with folic acid supplementation than without, thus providing added evidence of compliance with therapy. Serum folate activity was below the lower limit of normal (3–20 μg/l) only among those who did not receive folic acid supplements, the proportions so affected being 5% at the 28th week of pregnancy and 5% in the puerperium. Vitamin B_{12} deficiency did not occur.

Changes in maternal height

By 1–60 days after delivery, over 50% of the younger teenage girls were ≥2 cm taller than they were in early pregnancy, the increments ranging up to 16 cm. We compared the increases in maternal height in the five treatment groups A to E, considering the latter four treatments as a factorial experiment. There was no evidence of an association between antimalarial treatment and growth during pregnancy. The effect of adding iron was significant ($t = 2{\cdot}37$, $P = 0{\cdot}021$) and the folic acid supplementation approached conventional significance levels ($t = 1{\cdot}91$, $P = 0{\cdot}062$). However, the interaction between the two was also significant and negative ($t = -2{\cdot}02$, $P = 0{\cdot}048$) indicating that supplementation by iron or folic acid were equally effective and that providing both did not confer any extra benefit on change in maternal height compared with providing just one. The effect of supplementation of either kind was significant ($t = 2{\cdot}43$, $P = 0{\cdot}018$) with the mean height increases averaging 1·1 cm in groups A and B and 2·9 cm in the supplemented groups.

Because the distribution of maternal height gains was skew, with a few large values, the analysis was repeated using logistic regression to relate the proportions growing ≥2 cm to the treatment groups. The conclusions are virtually identical, except that both main effects were significant and the interaction only approached conventional significance. The overall effect of supplementation was highly significant ($t = 2{\cdot}82$, $P = 0{\cdot}007$). The proportions of girls who grew ≥2 cm were 29% for groups A and B and 71% of those receiving additional supplementation.

Table 5.3 shows the relation between mode of delivery and the distribution of maternal height in early pregnancy and in the puerperium. In Table 5.4, the changes in height are related to the five treatment groups. It is clear from both these tables that the distribution of height had changed during pregnancy. There was some suggestion that shorter girls grew faster than taller girls but Table 5.5 shows that this was only in those who took antimalarial drugs combined with one or both of the nutritional supplements (groups C, D and E).

Two girls, both aged 15 years, had a growth spurt during the period of observation, and in one the growth spurt certainly occurred entirely during pregnancy. When seen for the first time, she was about 18 weeks pregnant and 146 cm tall. She received iron supplements and antimalarial drugs. Towards the end of pregnancy, the change in her stature was so striking that on the day following normal delivery of a 2·90 kg female baby, her height was measured and found to be 162 cm. This change in height had occurred in only 117 days. Although she did not take folic acid supplements, she was never folate deficient throughout pregnancy and her serum and red blood cell folate levels at the end of pregnancy, 13 and 380 µg/l respectively, were among the highest in the series. Her haematocrit at delivery was 0·39 compared with 0·35 at booking. The second girl was on antimalarial drugs and folic acid supplements and her serum and red cell folate levels reached 13·8 and 321 µg/l respectively at the 36th week of gestation At booking her haematocrit was 0·46, falling to 0·39 in the puerperium. Her height increased from 155 to 165 cm over a period of 211 days from the 18th week of pregnancy to 49 days after a normal delivery. At birth, her male baby weighed 2·55 kg.

Table 5.3. Mode of delivery by maternal height at booking and in the puerperium

Mode of delivery	Period of measurement	No. of girls in height-groups (cm)					
		≤146	147–149	150–153	154–157	158–160	≥161
Spontaneous vaginal	Booking	2	3	7	17	10	9
	Puerperium	0	2	2	16	14	14
Forceps	Booking	1	0	1	1	0	0
	Puerperium	1	0	0	1	0	1
Caesarean section	Booking	3	0	3	2	0	0
	Puerperium	3	0	1	2	2	0
Total	Booking	6	3	11	20	10	9
	Puerperium	4	2	3	19	16	15

Table 5.4. Treatment schedule and distribution of maternal height at booking and in the puerperium

Treatment group	Period of measurement	No. of girls in height-groups (cm)					
		≤146	147–149	150–153	154–157	158–160	≥161
A Placebo	Booking	0	0	2	4	1	3
	Puerperium	0	0	0	5	1	4
B Antimalarials only	Booking	1	2	3	4	6	2
	Puerperium	1	1	2	3	8	3
C. Antimalarials and iron	Booking	3	1	2	4	0	2
	Puerperium	2	0	1	3	3	3
D. Antimalarials and folic acid	Booking	2	0	0	6	1	1
	Puerperium	1	1	0	3	3	2
E Antimalarials iron and folic acid	Booking	0	0	4	2	2	1
	Puerperium	0	0	0	5	1	3
Late teenage girls	Booking	1	0	5	2	0	2
	Puerperium	1	0	4	3	0	2

Table 5.5. Relation between maternal height increase (cm) and height at booking

Height at booking (cm)	Treatment groups			
	A and B		C, D and E	
	Mean height increase (cm)	Number	Mean height increase (cm)	Number
≤149	1·00	3	4·00	6
150–154	1·00	7	3·22	9
155–159	1·09	11	2·36	11
≥160	1·29	7	2·20	5
Total	1·11	28	2·90	31

The pooled standard deviation is 2·56 cm.

Relation between blood indices, blood folate levels, fetal birthweight, maternal weight gain and change in maternal height

The correlation of fetal birthweight and changes in maternal height with levels of serum and red blood cell folate, and haematocrit during various periods of pregnancy and in the puerperium was examined. Fig. 5.1 shows the relation between increase in height and the haematocrit level at 28 weeks of pregnancy (r = 0·431, n = 48, P = 0·002). There was also an additional effect of supplementation *per se*; those supplemented grew on average 1·1 cm (t = 2·11, P = 0·04) more than the unsupplemented after taking into account the relation with haematocrit. Two other significant correlations were those between fetal birthweight and serum folate activity at the end of pregnancy (r = 0·477, n = 22. P = 0·017; Fig. 5.2) and between increase in height and mean weekly weight gain from the first to the last attendance in the supplemented group (r = 0·503, d.f. = 29, P<0·01; Fig. 5.3) but not in the non-supplemented group (r = 0·32, P>0·5). The mean weight gain was 366 (SD 155) g in the spplemented group and 297 (SD 157) g in the non-supplemented group, a difference which just failed to reach statistical significance (t = 1·696, P>0·05).

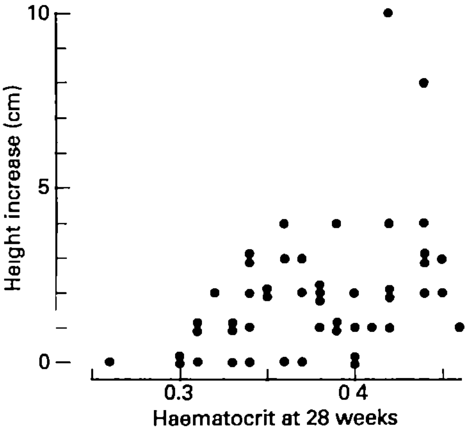

Fig. 5.1. Relation between increase in maternal height during pregnancy and the haematocrit level at the 28th week of pregnancy in early teenage primigravidae.

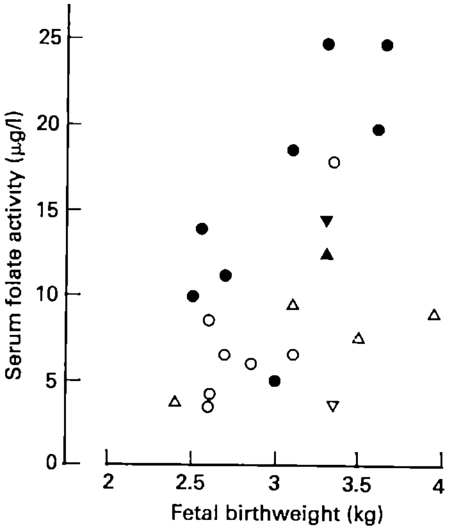

Fig. 5.2. Fetal birthweight and maternal serum folate activity at 36 weeks gestation in early teenage primigravidae With folic acid supplement: ● normal delivery, ▼ forceps, ▲ caesarean section. Without supplement· ○ normal delivery, ▽ forceps; △ caesarean section

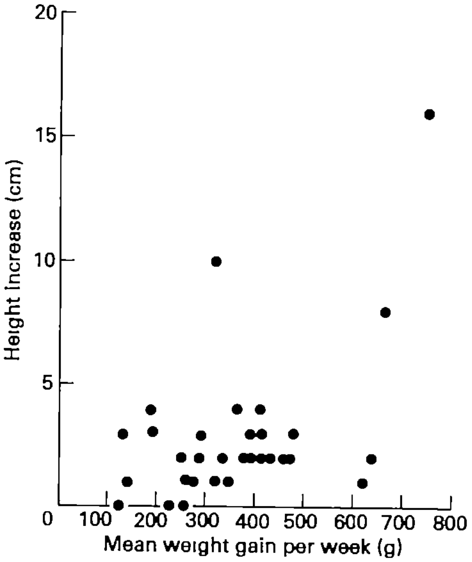

Fig. 5.3. Relation between maternal height increase during pregnancy and mean weight gain per week in primigravidae taking antimalarial drugs and nutritional supplements.

Pregnancy outcome

General characteristics

The data in Table 5.6 were derived from the following two sources: (i) all 59 teenage girls in treatment groups A to E in Table 5.1; (ii) all girls who were aged 16 years or less among the group of 38 girls earlier excluded from the analysis simply because their heights were not measured in the puerperium (32 in all). By combining the data from both sources, a better picture of the obstetric problems of early teenage Hausa girls was obtained

Malaria and anaemia were both common and eclampsia was not entirely preventable. These pregnant early teenagers were on the whole short in stature and although their weight gain was adequate (300–400 g/week) by Western standards, their babies were lighter at birth. Nearly 30% of the babies were born at home without expert supervision and were therefore not weighed. This default rate may appear high in Western eyes, but it is low by Third World standards.

Both contracted pelvis and disproportion were diagnosed clinically at the 36th–38th week of pregnancy and during labour. In contracted pelvis, the diagonal conjugate was always <10 cm. Disproportion was diagnosed by the head fitting test and by the pattern of cervical dilatation and moulding of the fetal head during trial labour (Philpott 1982*a*). Of the 11 girls with disproportion, one was found on admission to have intrauterine fetal death. Craniotomy was therefore performed Of the remaining 10, all were treated by trial labour, seven had caesarean section, two were delivered spontaneously and in one delivery was by forceps. Other indications for forceps delivery were delay in the second stage of labour (1), poor maternal effort (2) and intrapartum pre-eclampsia (1). There were two early neonatal deaths, one from asphyxia following a forceps delivery and the other from diarrhoea.

Combined effect of antimalarial chemoprophylaxis and nutritional supplementation

Table 5.6 presents the pregnancy complications, mode of delivery and fetal outcome in the five groups of girls. There were no significant differences between the five groups for most of the indices, although those receiving supplements (groups C, D, E) had generally better outcomes. In particular the variation in the proportions needing caesarean sections or destructive operations for disproportion was highly significant (log likelihood ratio = 13·4, d.f. = 4, $P = 0{\cdot}01$) with lower values for groups D and E.

Table 5.6. Pregnancy complications and outcome in five treatment groups

	Treatment group				
	A	B	C	D	E
Number of girls	14	23	17	21	16
Mean (SD) height at booking (cm)	156·0 (4·2)	155·8 (5·6)	154·4 (6·4)	155·3 (5·8)	156·4 (4·0)
Malaria at first attendance	4	6	6	3	6
Anaemia	1	5	1	2	3
Urinary tract infection	0	1	0	0	0
Pre-eclampsia	1	5	2	6	3
Eclampsia	2	1	2	0	1
Contracted pelvis	3	4	3	0	1
Cephalopelvic disproportion	4	3	3	0	1
Mode of delivery					
Spontaneous vertex	9	19	13	19	15
Forceps	1	1	1	1	1
Breech	0	1	0	0	0
Caesarean section					
for disproportion	3	1	3	0	0
for other reasons	0	1*	0	1†	0
Embryotomy	1	0	0	0	0
Mean (SD) fetal birthweight (kg)	2·92 (0·54)	2·78 (0·39)	2·80 (0·29)	2·88 (0·61)	2·92 (0·38)
Number weighed	8	15	10	18	14
Abdominal delivery + destructive operation	28·6%	8·7%	17·6%	4·8%	0
Operations for disproportion	28·6%	4·3%	17·6%	0	0

For details of treatment groups see Table 5·1

* Unfavourable cervix.

† Failed induction of labour for pre-eclampsia.

Discussion

Of the points that have emerged from this work, two stand out. One is that under certain circumstances, teenage primigravidae continue to grow taller during pregnancy. The other is that during the natural course of their pregnancies there is a link between nutritional supplementation and maternal skeletal growth.

At this stage, one critical comment ought to be made about the changes in maternal height reported here. Ideally, each teenage girl should have had her height measured at least twice during the same pregnancy. If that had been done the claim that teenage girls continue to grow taller during pregnancy would have been irrefutable. By measuring their heights only once during pregnancy and repeating the measurement in the puerperium as we did, the possibility that the reported changes in maternal height did in fact take place in the puerperium cannot be entirely ruled out. For one thing, fetal demands for nutrients probably take precedence over maternal requirements and so maternal growth may well have ceased temporarily during pregnancy and then proceeded at an accelerated pace ('catch-up') after the birth of the baby. But equally, we cannot dismiss the possibility that the demands imposed by lactation would also limit the nutrients that are available for maternal skeletal growth in the puerperium. Whatever the arguments, the point at issue is whether maternal skeletal growth occurs or not during pregnancy and the evidence suggests that it does. The case of the girl who grew the fastest in the series, entirely during her pregnancy, should dispel any doubts that growth spurts do occur during pregnancy. The observation that maternal height increase was very highly correlated with haematocrit at the 28th week of pregnancy (rather than later or during the puerperium) suggests that the growth was actually taking place soon after supplementation before competition from the fetus.

Among the local Hausas, with living conditions similar to those of the teenage girls reported here, the mean height of women of childbearing age who have finished growing is 157·2 cm (5 ft 2 in), compared with the mean values of 154·8 cm in early pregnancy and 156·4 in the puerperium in these young teenagers. The indications are, therefore, that these teenagers had not finished growing when they became pregnant and that their skeletal growth continued even during pregnancy—an observation which raises several interesting points. Under normal conditions, blood oestrogen concentration rises during pregnancy and its action ought to lead to an early epiphyseal closure and cessation of any further growth in maternal stature. In practice, however, skeletal growth did continue during pregnancy, and one possible explanation is the anti-oestrogenic effect which progesterone may well have exerted in these girls.

Moerman (1982) showed that below the age of 18 years, maternal height may not necessarily give as good an indication of the size of the bony birth canal as it does after that age. This is because the development of the bony birth canal is slower than that of maternal height during the early teenage period and the canal does not reach mature size until about 2–3 years after growth in height has ceased. Those findings, taken together with the ones presented in this clinical trial, make it clear that in teenage girls maternal height cannot be used in predicting obstetric performance in the same way as is customarily done for pregnant women who have finished growing. The best that can be done in these instances is to measure the heights twice, once in early pregnancy and again in the last 4 weeks of pregnancy, restricting the use of the first measurement merely to screening purposes, while employing the second in determining the relation between maternal size and outcome of labour.

The indications are that protecting these young teenage pregnant girls from malaria and adding nutritional supplements to their diets enhanced both maternal and fetal growth. It is also apparent that this acceleration of growth was associated with a statistically significant reduction in the proportion of those who had to have abdominal deliveries. Further data in support of these results are presented in the next chapter.

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6. Relations between maternal height, fetal birthweight and cephalopelvic disproportion suggest that young Nigerian primigravidae grow during pregnancy

in collaboration with C. E. ROSSITER & H. CHONG

Summary. The outcome of pregnancy was compared in 1065 booked and 1216 unbooked (emergency admissions) Hausa–Fulani primigravidae, half of them aged 10–16 years. The height of every woman was measured only once; this was either in early pregnancy in the booked primigravidae (range 122–176 cm) or at delivery in the unbooked primigravidae (range 130–186 cm). Mean fetal birthweights differed very significantly, being 2·91 kg and 2·76 kg for the booked and unbooked primigravidae respectively. The prevalence of cephalopelvic disproportion and of delivery by caesarean section or embryotomy were 9% and 11% respectively for the booked and 30% and 30% for the unbooked. There were two reasons why the booked primigravidae were less likely to develop cephalopelvic disproportion despite producing bigger babies; one was selection bias in the unbooked and the other (and more important) was growth of a teenage primigrivadae during pregnancy.

In chapter 5 which described a clinical trial of diet supplementation with iron and folic acid in early teenage pregnancy, growth in height during pregnancy was reported. Nutritional supplements not only enhanced growth both in the pregnant girl and her fetus but were also associated with a reduction in the prevalence of cephalopelvic disproportion. This chapter confirms that antenatal care greatly improves pregnancy outcome in teenage primigravidae, partly by promoting both maternal and fetal growth and at the same time by reducing the need for operative delivery.

Design of the analysis

The records studied were those of all Hausa–Fulani primigravidae with singleton babies who gave birth in hospital rather than at home, and with complete data on maternal age, maternal height and booking status. Attention was concentrated on the Hausa–Fulani only, because early teenage pregnancy rarely occurred among the other groups. A total of 2281 girls (1065 booked and 1216 emergency admissions) met these criteria, but, the fetal weight was not recorded in six of them Those who had antenatal care (booked group) first visited hospital when they were around 20 weeks pregnant on average. Their heights were measured at this initial visit and from then onwards until the puerperium they were placed on the following drugs: chloroquin (600 mg in a single dose) to clear existing malarial parasitaemia, pyrimethamine (25 mg weekly), ferrous sulphate (200 mg daily) and folic acid (5 mg daily). By contrast, the unbooked women had received no antenatal care and they were usually seen for the first time in labour, none having received any protection against malaria or against deficiencies of iron and folic acid in pregnancy. Their heights were measured for the first time within 10 days after delivery.

Pelvic assessment was carried out digitally at the end of pregnancy or in labour on every woman and contracted pelvis was diagnosed when the diagonal conjugate was <10 cm. Cephalopelvic disproportion was diagnosed by the head fitting test and by the pattern of cervical dilatation and moulding of the fetal head during trial labour.

Statistical methods

For tabulation the women were subdivided into six age and five height groups and by whether they had received antenatal care. However, for analysis, maternal age was combined into nine groups: ≤13 years, 14, 15, 16, 17–19, 20–24, 25–29, 30–34 and ≥35 years. Maternal height was combined into 10 groups: ≤1·34, 1·35–1·39, . . . 1·70–1·74 and ≥1·75 m.

To investigate the relations between the proportions of women with particular conditions, logistic regression was used (Cox 1970). This permits assessment of the association between the proportions and each explanatory index—maternal age, height or antenatal care—allowing for the other two indices.

Unbalanced analysis of variance was used to investigate the variability of fetal birthweight.

The computer packages used were P-STAT (P-STAT Inc.) to extract the necessary variables from the complete dataset, MINITAB (Minitab Project) to create the tables and GLIM (Numerical Algorithms Group) for the logistic regression and analyses of variance (see chapter 2).

Results of the analysis

Distribution of the women

Table 6.1 shows the distribution of the women according to their height, age and booking status It is clear that at each age the women who were unbooked tended to be shorter than the booked women. Moreover, under the age of 20 years, the booked women of any particular age group and the unbooked of the next older group had similar height distributions.

Maternal age, height, antenatal care and mode of delivery

Figs. 6.1 and 6.2 and Appendices 6.1 and 6.2 show that the youngest and the shortest women both had the highest prevalence of contracted pelvis, they were at the greatest risk of developing cephalopelvic disproportion and of requiring delivery by caesarean section or embryotomy. With increasing maternal age and height, the rates of these three pregnancy complications fell and the rates for women in the booked group were much less than the rates for women in the unbooked group in the majority of the height and age subgroups. The tallest women, irrespective of their age and booking status, rarely had contracted pelvis or cephalopelvic disproportion.

Fig. 6.2 shows that the rates of contracted pelvis, cephalopelvic disproportion and caesarean section plus embryotomy were very similar among the teenage girls. This was because among the teenagers, cephalopelvic disproportion was by far the commonest indication for caesarean section, whereas in the oldest women, the operation was increasingly performed for reasons other than cephalopelvic disproportion (Appendix 6.2)

Logistic regression confirms that the association with maternal height accounts for much more of the variation in the caesarean section plus embryotomy rate. Nevertheless, even after allowance for height, age still contributes significantly ($\chi^2 = 38$, d.f. = 9, $P<0{\cdot}0001$). The logistic regression also shows the major importance of the acceptance of antenatal care as the rate was much higher in those who did not seek it and were admitted as emergencies (t = 9·3, d.f = 2262, $P \ll 0{\cdot}0001$).

Other deliveries (breech, forceps, etc.) showed no significant association with maternal age, height or antenatal care so the variation in the spontaneous delivery rate (Appendix 6.2) directly reflects the variation in the rate of caesarean sections plus embryotomies.

Antenatal care and pregnancy complications

Table 6 2 lists the pregnancy complications observed in the booked and unbooked groups. The striking difference was in the disproportion rates: this was not surprising since the presence of cephalopelvic disproportion was the principal reason why the unbooked women reported to hospital in the first place. The number of women delivered at home and who did not come to the hospital is unknown and this prevents proper comparison between the booked women and those admitted as an emergency (unbooked group).

Birthweight

In Appendix 6.3, the mean fetal birthweights are shown for each of the 60 age–height–booking

Table 6.1. Maternal age, height and booking status

Maternal height (m)	Maternal age (years)											
	<15		15		16		17–19		20–24		≥25	
	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked
≤1·49	82	44	86	47	38	29	71	26	28	15	6	5
	(53·2)	(34·1)	(32·5)	(19·0)	(22·0)	(15·9)	(20·6)	(8·8)	(13·9)	(9·9)	(7·6)	(8·3)
1·50–1·54	42	40	101	91	62	57	119	83	77	31	26	13
	(27·3)	(31·0)	(38·1)	(36·7)	(35·8)	(31·3)	(34·6)	(28·2)	(38·3)	(20·4)	(32·9)	(21·7)
1·55–1·59	22	28	61	74	43	54	94	96	59	54	27	17
	(14·3)	(21·7)	(23·0)	(29·8)	(24·8)	(29·7)	(27·3)	(32·7)	(29·4)	(35·5)	(34·2)	(28·3)
1·60–1·64	6	13	16	29	23	35	47	64	29	31	14	17
	(3·9)	(10·1)	(6·0)	(11·7)	(13·3)	(19·2)	(13·7)	(21·8)	(14·4)	(20·4)	(17·7)	(28·3)
≥1·65	2	4	1	7	7	7	13	25	8	21	6	8
	(1·3)	(3·1)	(0·4)	(2·8)	(4·0)	(3·8)	(3·8)	(8·5)	(4·0)	(13·8)	(7·6)	(13·3)
Total	154	129	265	248	173	182	344	294	201	152	79	60
Mean height (m)	1·50	1·52	1·52	1·54	1·54	1·55	1·54	1·56	1·54	1·58	1·56	1·58

Results are numbers of women with percentages shown in parentheses

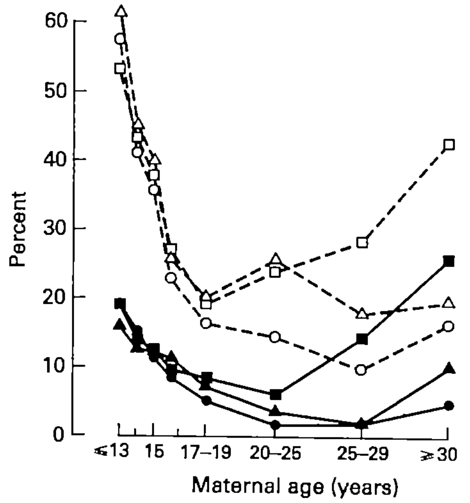

Fig. 6.1. Maternal age, booking status, incidence of contracted pelvis (● ○), cephalopelvic disproportion (▲ △) and the caesarean section–embryotomy rates (■ □) in Hausa–Fulani primigravidae Solid lines and symbols: booked; dashed lines and open symbols: unbooked

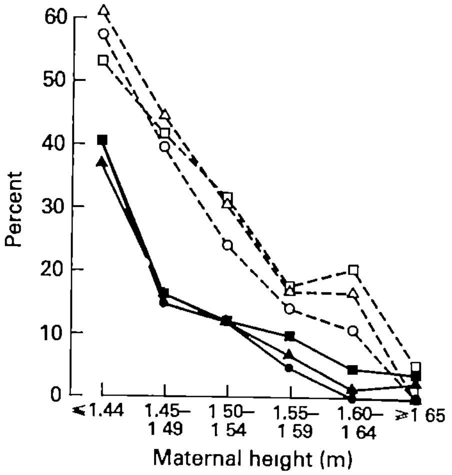

Fig. 6.2. Maternal height, booking status, incidence of contracted pelvis (● ○), cephalopelvic disproportion (▲ △) and the caesarean section–embryotomy rates (■ □) in Hausa–Fulani primigravidae Solid lines and symbols booked, dashed lines and open symbols· unbooked

Table 6.2. Hausa–Fulani primigravidae: relation between pregnancy complications and booking status

Complication	Unbooked group (n = 1216)	Booked group (n = 1065)
Anaemia (haematocrit <0·30)*	115 (9·5)	92 (8·6)
Associated diseases		
Infective	26 (2·1)	20 (1·9)
Non-infective	22 (1·8)	11 (1·0)
Pre-eclampsia	176 (14·5)	139 (13·1)
Eclampsia	88 (7·2)	64 (6·0)
Placenta praevia	8 (0·7)	2 (0·2)
Placental abruption	3 (0·2)	2 (0·2)
APH—other causes	15 (1·2)	5 (0·5)
Breech presentation	44 (3·6)	20 (1·9)
Occipitoposterior	93 (7·6)	45 (4·2)
Face or brow	5 (0·4)	1 (0·1)
Postpartum haemorrhage	31 (2·5)	21 (2·0)
Retained placenta	9 (0·7)	2 (0·2)
Cord prolapse	8 (0·7)	4 (0·4)
None of the above	693 (57·1)	712 (66·9)
Cephalopelvic disproportion	361 (29·7)	100 (9·4)

Results are numbers of women with percentages in parentheses
* Three values not known in the unbooked group.

status subgroups. The birthweight was on average 0·13 kg higher for the booked women who received antenatal care (t = 6·1, d.f. = 2271, P <0·0001), allowing for maternal age and height. It is also clear that fetal birthweight increased with increasing maternal height, but there appears to be little relation to maternal age. Analysis of variance confirms that there is no significant association with maternal age, allowing for booking status and maternal height. The regression of fetal birthweight on maternal height was very highly significant ($t = 7{\cdot}6$, $P < 0{\cdot}0001$) indicating an increase of 13 g for each cm increase in maternal height. This increase did not depend ($t = 0{\cdot}5$) on the booking status.

Fetal outcome

Appendix 6.4 shows the relation between maternal characteristics and fetal outcome. Logistic regression analysis of live birth, stillbirth and neonatal death rates on maternal height, age and booking status gave the following results. The proportion of live births is consistently higher in the booked women who received antenatal care ($t = 6{\cdot}46$, d.f. = 2262, $P < 0{\cdot}0001$) and the rate also increases with increasing height ($\chi^2 = 21$, d.f. = 9, $P = 0{\cdot}013$). There appears to be little relation with age.

The stillbirth rate also shows a significant relation to booking status ($t = 6{\cdot}32$, $P < 0{\cdot}001$), an almost significant relation to height ($\chi^2 = 16$, d.f = 9, $P = 0{\cdot}07$) but none to age.

Neonatal deaths just show a marginally significant association with booking status ($t = 2{\cdot}21$, $P = 0{\cdot}03$).

Discussion

During child-bearing, the advantages tall women have over short women are very evident in these Nigerian primigravidae, and in this particular respect, some of the findings reported here confirm existing knowledge (Baird 1949). For example, the fact that antenatal care greatly improved fetal survival was expected (chapter 3). However, the real point of interest and one that requires explanation is why early teenage girls who are <160 cm in height have less risk of cephalopelvic disproportion if they receive antenatal care and hence produce bigger babies (Figs. 6.1 and 6.2 and Appendix 6.1).

At this point, it is important to recall that the heights of the women were measured in early pregnancy in the booked group, and in labour or immediately postpartum in the unbooked emergency group The clinical trial of diet supplementation with iron and folic acid indicated that treated girls aged ≤16 years grew 4 cm on average between booking and delivery (chapter 5). As all the booked women in this study were provided with these supplements, they would be expected also to be taller on average at delivery. To investigate the effect of this, 4 cm was added to the height of all such young booked women and the relation of cephalopelvic disproportion to adjusted height was reassessed. Fig. 6.3 shows the results compared to the unadjusted rates for both the booked and unbooked women. The cephalopelvic disproportion rate in the very short women (<1·5 m) rose markedly towards the rate found in the unbooked women. This suggests that the assumption of growth during pregnancy accounts for a good proprortion of the difference in the cephalopelvic disproportion rates, although selection bias clearly is an important factor.

These results suggest that with improvements in maternal health brought about by nutritional supplements and malaria chemoprophylaxis, the teenage Nigerian girl who receives antenatal care grows during pregnancy so that at delivery, her skeletal size is no longer the same as it was earlier in pregnancy. Clearly, these results taken together with those of the clinical trial reported in chapter 5 raise wider issues. Obstructed labour from cephalopelvic disproportion is common in impoverished areas (Mtimavalye *et al.* 1974; Naeye *et al.* 1977), especially in societies where child-bearing commonly starts before full physical maturity is attained. To reduce the prevalence of obstructed labour in our societies, it is

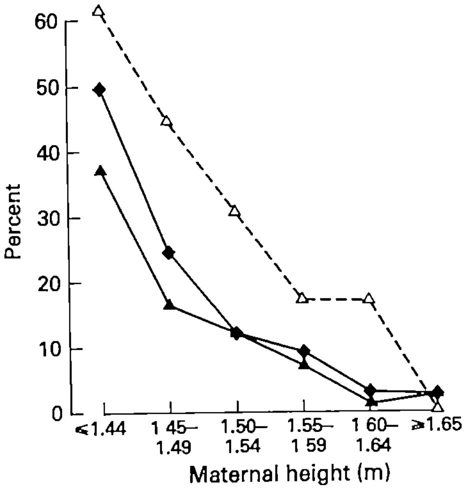

Fig. 6.3. Relation between cephalopelvic disproportion, booking status and height at booking (▲ △) or height adjusted for growth during pregnancy (◆). Solid lines and symbols booked; dashed lines and open symbols. unbooked.

necessary to discourage early teenage marriage and to delay child-bearing until the age of 17–19 years. Another approach would be to encourage such high-risk girls to receive antenatal care during which nutritional supplements and malarial chemoprophylaxis (in endemic areas) are given for the specific purpose of accelerating maternal skeletal growth. In this regard, the earlier in pregnancy such supplements are used, the more effective will such a public health measure be in reducing the prevalence of difficult labour and its consequences, especially vesicovaginal fistula. The results might even be best if these preventive measures—that is, good nutrition and improved health care—are applied on a wide scale during child development. This has already happened in affluent societies and it provides one explanation why dystocia is rare among early teenage primigravidae in affluent societies (Bremberg 1977; Sandstrom 1977) but common wherever socioeconomic deprivation exists on a large scale (Scher & Utian 1970).

Appendix 6.1. Prevalence of contracted pelvis and cephalopelvic disproportion by maternal age, height and booking status

Maternal age (years)	Maternal height (m)	Number of women		Prevalence of contracted pelvis (%)		Prevalence of cephalopelvic disproportion (%)	
		Unbooked	Booked	Unbooked	Booked	Unbooked	Booked
<15	≤1·49	82	44	58·5	29·5	61·0	25·0
	1·50–1·54	42	40	28·6	17·5	33·3	15·0
	1·55–1·59	22	28	27·3	3·6	31·8	3·6
	1·60–1·64	6	13	33·3	0	50·0	0
	≥1·65	2	4	0	0	0	0
15	≤1·49	86	47	54·6	19·1	54·6	19·1
	1·50–1·54	101	91	33·7	15·4	40·6	14·3
	1·55–1·59	61	74	18·0	8·1	26·2	10·8
	1·60–1·64	16	29	18·7	0	18·7	3·4
	≥1·65	1	7	0	0	0	14·3
16	≤1·49	38	29	42·1	17·2	47·4	17·2
	1·50–1·54	62	57	27·4	15·8	29·0	17·5
	1·55–1·59	43	54	13·9	3·7	13·9	5·6
	1·60–1·64	23	35	4·3	0	13·0	0
	≥1·65	7	7	0	0	0	14·3
17–19	≤1·49	71	26	19·7	3·8	29·6	7·7
	1·50–1·54	119	83	21·0	10·8	24·4	12·0
	1·55–1·59	94	96	16·0	6·2	14·9	8·3
	1·60–1·64	47	64	6·4	0	8·5	3·1
	≥1·65	13	25	0	0	0	0
20–24	≤1·49	28	15	35·7	20·0	46·4	26·7
	1·50–1·54	77	31	13·0	0	28·6	0
	1·55–1·59	59	54	8·5	0	16·9	3·7
	1·60–1·64	29	31	17·2	0	24·1	0
	≥1·65	8	21	0	0	0	0
≥25	≤1·49	6	5	33·3	20·0	50·0	40·0
	1·50–1·54	26	13	23·1	0	34·6	0
	1·55–1·59	27	17	3·7	5·9	0	5·9
	1·60–1·64	14	17	7·1	0	17·6	0
	≥1·65	6	8	0	0	0	0

Appendix 6.2. Mode of delivery (%) by maternal age, height and booking status

Maternal age (years)	Maternal height (m)	Number of women		Spontaneous delivery (%)		Caesarean + embryotomy (%)		Other deliveries (%)	
		Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked
<15	≤1·49	82	44	31·7	68·2	56·1	25·0	12·2	6·8
	1 50–1·54	42	40	57·1	72·5	33·3	12·5	9·5	15·0
	1·55–1·59	22	28	59·1	75·0	31·8	10·7	9·1	14·3
	1 60–1·64	6	13	33·3	92·3	50·0	7·7	16·7	0
	≥1 65	2	4	100·0	100·0	0	0	0	0
15	≤1·49	86	47	41·9	76·6	48·8	17 0	9·3	6·4
	1·50–1·54	101	91	46·5	72·5	42·6	14·3	10·9	13·2
	1·55–1·59	61	74	63·9	83·8	22·9	10·8	13·1	5·4
	1·60–1·64	16	29	81·2	89·7	12·5	6·9	6·2	3·4
	≥1·65	1	7	100·0	85·7	0	14·3	0	0
16	≤1·49	38	29	60·5	72·4	36·8	20·7	2·6	6·9
	1·50–1·54	62	57	54·8	82·5	33·9	14·0	11·3	3·5
	1·55–1·59	43	54	62·8	88 9	20·9	5·6	16·3	5·6
	1·60–1·64	23	35	73·9	85·7	13·0	0	13·0	14·3
	≥1·65	7	7	100·0	71·4	0	14·3	0	14·3
17–19	≤1·49	71	26	62·0	84·6	29·6	7·7	8·4	7·7
	1·50–1·54	119	83	70·6	79 5	23·5	10 8	5·9	9·6
	1·55–1·59	94	96	73·4	85·4	13·8	11·5	12·8	3·1
	1·60–1·64	47	64	83·0	85·9	8·5	4·7	8·5	9·4
	≥1·65	13	25	76·9	92·0	7 7	4·0	15·4	4·0
20–24	≤1·49	28	15	57·1	46·7	42·9	26·7	0	26·7
	1·50–1·54	77	31	61·0	90·3	24·7	6·4	14·3	3·2
	1·55–1·59	59	54	69·5	85·2	15·2	7·4	15·2	7·4
	1·60–1·64	29	31	62·1	93 5	31·0	0	6·9	6·4
	≥1·65	8	21	87·5	100·0	0	0	12·5	0
≥25	≤1·49	6	5	16·7	20·0	66·7	60·0	16·7	20·0
	1·50–1·54	26	13	50 0	84 6	46·2	15·4	3·8	0
	1·55–1·59	27	17	74·1	58·8	11·1	17·6	14·8	23·5
	1·60–1·64	14	17	42·9	76·5	50·0	17 6	7 1	5·9
	≥1·65	6	8	83·3	75·0	16·7	0	0	25·0

Appendix 6.3. Distribution of fetal birthweight by maternal age, height and booking status

Maternal age (years)	Maternal height (m)	Number of women		Mean fetal weight (kg)	
		Unbooked	Booked	Unbooked	Booked
<15	≤1·49	81	44	2·56	2·77
	1·50–1·54	42	40	2·68	2·80
	1·55–1·59	22	28	2·77	2·72
	1·60–1·64	6	13	3·22	2·76
	≥1·65	2	4	3·45	2·81
15	≤1·49	86	47	2·78	2·73
	1·50–1·54	100	91	2·79	2·91
	1·55–1·59	61	74	2·65	2·97
	1·60–1·64	16	29	2·86	3·01
	≥1·65	1	7	2·90	3·33
16	≤1·49	38	28	2·65	2·80
	1·50–1·54	62	57	2·75	2·83
	1·55–1·59	43	54	2·79	2·96
	1·60–1·64	23	35	2·76	2·97
	≥1·65	7	7	3·24	3·21
17–19	≤1·49	71	26	2·64	2·75
	1·50–1·54	119	82	2·79	2·98
	1·55–1·59	94	96	2·74	2·96
	1·60–1·64	47	64	2·92	3·04
	≥1·65	13	25	2·77	2·95
20–24	≤1·49	28	15	2·53	2·78
	1·50–1·54	77	31	2·77	2·90
	1·55–1·59	59	54	2·89	2·98
	1·60–1·64	28	31	2·81	3·04
	≥1·65	8	21	3·02	2·92
≥25	≤1·49	6	5	2·86	2·85
	1·50–1·54	26	12	2·80	2·59
	1·55–1·59	27	17	2·72	3·07
	1·60–1·64	14	17	2·82	2·75
	≥1·65	6	8	3·52	3·27

Appendix 6.4. Fetal outcome (%) by maternal age, height and booking status

Maternal age (years)	Maternal height (m)	Number of women		Livebirths (%)		Stillbirths (%)		Neonatal deaths (%)	
		Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked
<15	≤1·49	82	44	73·2	88·6	12·2	6·8	14·6	4·5
	1·50–1·54	42	40	88·1	92·5	9·5	0	2·4	7·5
	1·55–1·59	22	28	86·4	92·9	13·6	3·6	0	3·6
	1·60–1·64	6	13	100·0	100·0	0	0	0	0
	≥1·65	2	4	100·0	100·0	0	0	0	0
15	≤1·49	86	47	87·2	95·7	8·1	4·3	4·6	0
	1·50–1·54	101	91	68·3	90·1	17·8	1·1	13·9	8·8
	1·55–1·59	61	74	82·0	94·6	11·5	0	6·6	5·4
	1·60–1·64	16	29	87·5	96·5	6·2	0	6·2	3·4
	≥1·65	1	7	100·0	100·0	0	0	0	0
16	≤1·49	38	29	81·6	96·5	15·8	0	2·6	3·4
	1·50–1·54	62	57	80·6	87·7	12·9	7·0	6·4	5·3
	1·55–1·59	43	54	79·1	96·3	4·6	1·8	16·3	1·8
	1·60–1·64	23	35	87·0	91·4	8·7	0	4·3	8·6
	≥1·65	7	7	100·0	100·0	0	0	0	0
17–19	≤1·49	71	26	84·5	88·5	9·9	3·8	5·6	7·7
	1·50–1·54	119	83	82·3	92·8	6·7	6·0	10·9	1·2
	1·55–1·59	94	96	86·2	89·6	10·6	4·2	3·2	6·2
	1·60–1·64	47	64	89·4	93·7	4·3	3·1	6·4	3·1
	≥1·65	13	25	92·3	96·0	7·7	0	0	4·0
20–24	≤1·49	28	15	82·1	100·0	14·3	0	3·6	0
	1·50–1·54	77	31	85·7	96·8	5·2	0	9·1	3·2
	1·55–1·59	59	54	84·7	96·3	11·9	0	3·4	3·7
	1·60–1·64	29	31	89·7	90·3	6·9	3·2	3·4	6·4
	≥1·65	8	21	100·0	95·2	0	0	0	4·8
≥25	≤1·49	6	5	100·0	80·0	0	20·0	0	0
	1·50–1·54	26	13	84·6	92·3	7·7	0	7·7	7·7
	1·55–1·59	27	17	81·5	88·2	18·5	5·9	0	5·9
	1·60–1·64	14	17	92·9	88·2	7·1	0	0	11·8
	≥1·65	6	8	83·3	100·0	16·7	0	0	0

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7. Multiple pregnancy

in collaboration with C. E. ROSSITER

Summary. There were 357 twin pairs, six sets of triplets and one pair of conjoined twins born in the group of 15 020 booked women compared with 392 twin pairs, 10 sets of triplets, two sets of quadruplets and two sets of conjoined twins in the 7654 emergency admissions (unbooked women). Rising maternal age, parity and height were all associated with rising twinning rate. Maternal death rates were 0·8% for singleton pregnancies, 2·0% for twin pregnancies, 6·3% for triplet pregnancies and none for the two women who had quadruplets. The mean fetal birthweights were 3·08 kg for singletons, 2·28 kg for twins, 1·71 kg for triplets and 1·36 kg for quadruplet babies. Fetal loss was 10% for singletons, 24% for twins, 42% for triplets and 75% for quadruplet babies. The poorer maternal and fetal outcomes in multiple pregnancy compared with those in singleton pregnancy were due to the combined effects of certain pregnancy complications, including the retention of the second twin, of inadequacies in our health care facilities and of unfavourable socioeconomic circumstances especially lack of antenatal care.

The literature on multiple births under African and Third World conditions continues to grow (Rehan & Tafida 1980; Azubuike 1982; Marivate & Norman 1982; Nylander 1983). In this report emphasis is laid on the epidemiological aspects of multiple births, on the maternal and fetal outcomes, and on the phenomenon of retained second twin.

Frequency of multiple births

The total number of deliveries was 15 020 in the booked group and 7654 in the unbooked group. The number of multiple births and their frequencies in the survey population are shown in Appendix 7.1 and in Table 7.1. The rates in the unbooked group (emergency admissions) were higher than those in the booked group (Table 7.1). The rates in the booked group, but not in the emergency admissions, were fairly consistent with Hellin's hypothesis, which states that if twins occur every n births in a population, then triplets will occur every n^2 births, and quadruplets every n^3 births.

Twins

Epidemiological features

The sex of both twins was recorded on 729 occasions: both were males in 223 pairs, both females in 252 pairs and of unlike sex in 254 pairs. Detailed analysis was confined largely to the twin sets born in the booked group and where the sex of both babies was recorded. Knowing the number of like-sex and unlike-sex twin pairs, we applied Weinberg's formula to determine the monozygotic and dizygotic twinning rates in the booked women, relating these findings to maternal age and parity, to social factors, and to fetal birthweight.

Social factors

As expected, Table 7.2 shows that the monozygotic twinning rates were lower than the dizygotic twinning rates. For both types the rates for the social groups varied little, except for a small group of non-Nigerian mothers. They comprised Europeans, Asians and a few

Table 7.1. Frequency of multiple births in booked and unbooked women (emergency admission) in Zaria

	Booked group		Unbooked group	
	Number of sets	Frequency of multiple births	Number of sets	Frequency of multiple births
Twins	357	2·4 in 10^2	392	5·1 in 10^2
Triplets	6	4·0 in 10^4	10	13·1 in 10^4
Quadruplets	0	—	2	261 in 10^6
Conjoined twins	1	0·7 in 10^6	2	261 in 10^6

Table 7.2. Twin sex and zygosity rate by social factors in booked women

		Twinning rate/1000 deliveries				
Social factors	Total no. of deliveries	Like sex	Unlike sex	Monozygotes	Dizygotes	All twins
Residence						
Outside Zaria	1010	17·8	7·9	9·9	15·8	25·7
		(18)	(8)	(10)	(16)	(26)
Zaria	14 009	15·1	8·2	6·9	16·4	23·3
		(212)	(115)	(97)	(230)	(325)
Religion						
Christian	7156	15·9	6·3	9·6	12·6	22·2
		(114)	(45)	(69)	(90)	(159)
Islam	7170	15·3	10·0	5·3	20·1	25·4
		(110)	(72)	(38)	(144)	(182)
Ethnic group						
Hausa–Fulani	4485	15·6	10·7	4·9	21·4	26·3
		(70)	(48)	(22)	(96)	(118)
Other Nigerians	10 393	15·3	7·2	8·1	14·4	22·5
		(159)	(75)	(84)	(150)	(234)
Non-Nigerians	112	8·9	—	(8·9)	—	8·9
		(1)	(0)	(1)	(0)	(1)
Education						
Formal education	2376	17·7	6·3	11·4	12·6	24·0
		(42)	(15)	(27)	(30)	(57)
None	12 496	14·8	8·6	6·2	17·3	23·5
		(185)	(108)	(77)	(216)	(293)

Numbers of twin sets are shown in parentheses.

Africans from countries other than Nigeria and they had the lowest twinning rate of only 8·9 per 1000 births.

Maternal age and parity

Appendix 7.2 shows the influence of maternal age and parity on the twinning rate in those booked Nigerian women with complete data on age and parity. Twinning rates tended to rise both with increasing maternal age and with parity.

Variations in the monozygotic and dizygotic twinning rates with maternal age and with parity are shown in Fig. 7.1. The tendency of the dizygotic twinning rates to rise with increasing age and parity are evident. The monozygotic twinning rates were less affected.

Maternal height

Table 7.3 shows that among the monozygotes, the highest twinning rate was recorded in the tallest women, but with the small number

Table 7.3. Monozygotic and dizygotic twinning rates by maternal height in booked women

Maternal height (m)	Twinning rate/1000 deliveries		
	Monozygotes	Dizygotes	Total
≤1·54	5·6 (24)	14·9 (64)	20·5 (88)
1·55–1·59	7·4 (33)	14·3 (64)	21·7 (97)
1·60–1·64	4·9 (18)	21·3 (78)	26·2 (96)
≥1·65	9·6 (16)	19·1 (32)	28·7 (48)

Numbers of twin sets are shown in parentheses.

Table 7.4. Twinning rate by maternal height and age in booked women

Maternal age (years)	Twinning rate/1000 deliveries in height groups (m)			
	≤1·54	1·55–1·59	1·60–1·64	≥1·65
≤19	10·6 (14)	13·8 (15)	—	—
20–24	21·6 (29)	17·1 (25)	24·0 (30)	18·3 (10)
25–29	26·9 (26)	25·7 (30)	33·1 (34)	34·2 (18)
≥30	23·4 (14)	33·5 (24)	43·5 (29)	52·8 (17)

Numbers of twin sets are shown in parentheses

involved it is not possible to infer any trend. In the dizygotes, the twinning rate was consistently greater in the taller women.

In Table 7.4, the twinning rate was related to both maternal age and maternal height. At each of the height groups, twinning rates rose with increasing maternal age. Over the age of 25 years, there was a tendency for the twinning rate to rise with increasing maternal height. The height effect was almost entirely a function of the dizygotic twinning rate.

Mean fetal birthweights and fetal sex

Table 7.5 shows the mean fetal birthweights of the twins born in the booked group. On average, the second twins were slightly heavier than the first, and the females heavier than the males, but the differences were not significant.

Table 7.5. Mean fetal birthweight (kg) by sex and twin birth order

Birth order	Mean fetal birthweight (kg)	
	Males	Females
First twin	2·28	2·50
Second twin	2·32	2·55

Clinical features

In this section of the analysis, pregnancy complications and outcomes are compared in the booked and emergency admissions (unbooked). The booked women had all had some hospital antenatal care for periods varying between 4 and 20 weeks, whereas most of the unbooked women were seen for the first time when they were

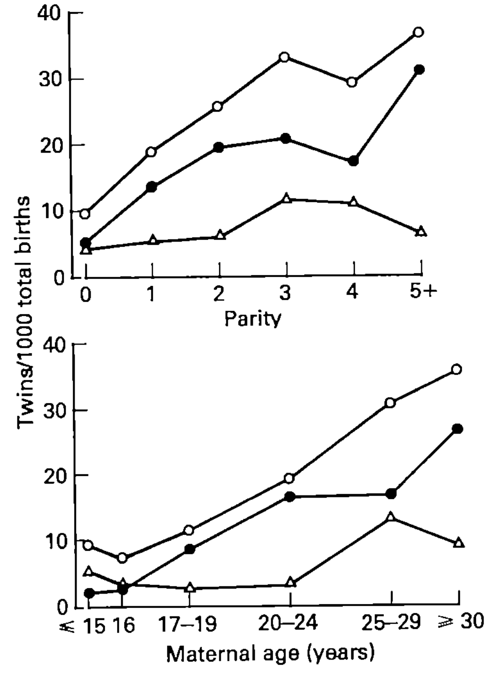

Fig. 7.1. Twinning rate, maternal age and parity △ Monozygotic; ● dizygotic; ○ total

already in labour or shortly afterwards, having had no antenatal care whatsoever. The number of women giving birth to twins at home is unknown. This prevents the statistical comparison of the booked women with those admitted as an emergency. Neverthelesss the comparison does provide insight into the problems encountered in twin pregnancy.

Pregnancy complications

Table 7.6 shows the frequency of various pregnancy complications in the booked and unbooked groups in singleton and twin pregnancies.

Anaemia, eclampsia and antepartum haemorrhage (APH) were far less frequent in the booked than in the emergency admissions. Among those with anaemia, the haematocrit was <0·19 in 3% of the booked and in 27% of the unbooked. The lower prevalence of hypertension and pre-eclampsia in the emergency admissions can be explained. On their own and when mild, both hypertension and pre-eclampsia are unlikely to cause unbooked Nigerian patients to seek expert care and so women with these particular complications were under represented.

Labour complications

Potentially fatal complications were more frequent in the unbooked than in the emergency admissions (Table 7.7). The common compli-

Table 7.6. Prevalence of pregnancy complications by booking status in singleton and twin pregnancies

	Prevalence of complication (%)			
	Singleton pregnancy		Twin pregnancy	
Pregnancy complications	Unbooked	Booked	Unbooked	Booked
Total no. of women	7273	14 657	381	353
Previous caesarean section	2·9	4·7	1·3	4·0
Other previous operations	0·9	3·6	0·0	4·0
Anaemia in pregnancy	11·5	5·4	15·7	6·5
Associated diseases				
Infective	1·5	1·8	0·5	2·3
Non-infective	1·0	1·1	0·8	0·8
Hydramnios	0·5	0·3	2·4	5·1
Pre-eclampsia	6·1	5·7	11·8	16·1
Hypertension	0·6	0·7	0·3	1·1
Eclampsia	5·0	0·9	3·7	1·4
Antepartum haemorrhage				
Placenta praevia	2·4	0·5	3·1	0·6
Placental abruption	2·0	0·3	0·8	0·8
Gishiri cut	0·8	0·0	1·0	0·0
Unclassified	1·9	0·7	1·0	0·3

Table 7.7. Prevalence of complications in labour and maternal outcome by booking status in singleton and twin pregnancies

	Prevalence of complication (%)			
	Singleton pregnancy		Twin pregnancy	
Characteristic	Unbooked	Booked	Unbooked	Booked
Total no of women	7274	14 667	381	353
Stage of labour on admission				
Not in labour	0·8	0·9	0·5	0·6
First stage	45·3	58 1	33·1	66·3
Second stage	13·8	6·9	8·1	7·4
Third stage	9·8	1·2	4·2	0·3
Early puerperium	8·3	1·4	39·4	5·9
Not stated	22·0	31·5	14·7	19·5
Contracted pelvis	10·1	2·4	1·6	0 6
Disproportion	14·6	3·9	0·8	0·3
Prolonged labour	13·1	1·7	6·8	1·4
Postpartum haemorrhage	4·9	1 6	9·2	4·2
Retained placenta	11·9	1·2	7·6	1·4
Manual removal of placenta	4·4	0·5	3·4	1·1
Uterine rupture	2·3	0·2	1 0	0 0
Gishiri cut	1·1	0·0	1·6	0 0
Episiotomy	11 0	11·2	3·4	6·2
Induction/augmentation of labour				
Amniotomy	1·3	1·2	1·0	2·0
Oxytocin	1·4	1·5	1·3	3·1
Blood transfusion	24·7	4·0	26·8	7·4
Maternal deaths	2·82	0·12	3·67	0·28

cations which forced the unbooked women to seek expert care were retained second twins, retained placenta, postpartum haemorrhage and prolonged labour. The proportion of women who reported at the second stage of labour and later was 52% for the emergency admissions and only 14% for the booked. In the face of such adverse conditions, 26·8% of all the twin pregnancies admitted as an emergency required blood transfusion compared with 7% in the booked group.

Place of birth

Twin pregnancies in the booked group were rarely delivered at home and fetal outcomes for the hospital births were much better than those for babies born at home before admission to hospital. Excluding the conjoined twins, and those with unrecorded sex, 1190 babies (672 booked and 518 unbooked) were born in hospital and 268 (34 booked and 234 unbooked) were born at home before admission to hospital. The number of perinatal deaths was 294 for babies born in hospital (103 booked and 191 unbooked) and 90 for babies born at home (nine booked and 81 unbooked), giving fetal loss rates of 15% and 37% for the booked and unbooked women who were delivered in hospital, and 27% and 35% for the booked and for the unbooked women (emergency admissions) who were delivered at home before admission to hospital.

Mode of delivery and fetal outcome

The data are shown in Appendix 7.3 and they exclude the 34 twin pairs in whom fetal sex was not recorded. There were striking differences between the booked and the emergency admissions and between the first and second twins. Fetal malpresentation (especially transverse lie), retained second twin, operative delivery (notably caesarean section, embryotomies and 'other deliveries') and also intrauterine death before admission all featured prominently. All these hazards were highest in frequency among the second twin of the emergency admissions, and least in the first twin of the booked women.

Fetal birthweight and outcome

Table 7.8 shows the distribution of birthweights in relation to fetal outcome among hospital twin births only. The overall mean fetal birthweight was 2·28 kg, and the proportion of babies with low birthweight (≤2·50 kg) was 62·9%. Live births were heavier than the others, and the neonatal deaths were the greatest contributors to the perinatal deaths.

Fig. 7.2 shows the birthweight-specific perinatal mortality rates for each mode of delivery. Irrespective of mode of delivery, perinatal mortality rate was >500 per 1000 total births for the low-birthweight babies. As in singleton births (chapter 11) increasing fetal birthweight was associated with a marked fall in death rate.

Retained second twin

There were 128 retained second twins in all, giving a frequency of 17% of all second twins in the survey population. Data were sparse in four out of these 128 retained second twins and so these four have been excluded from further detailed analyses. In the remaining 124 retained second twins the birth place of the matching first twin was in hospital in eight and outside hospital in 116, of which 71 were from outside Zaria. Where the first twin was born outside Zaria, the

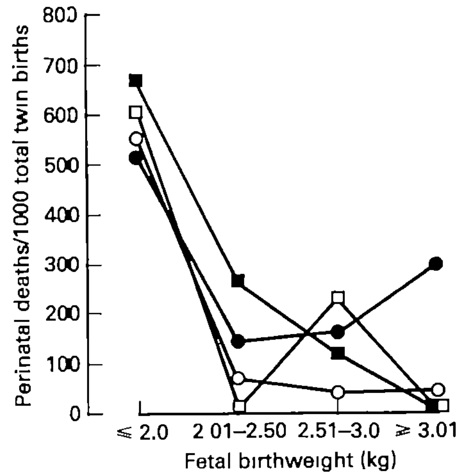

Fig. 7.2. Fetal birthweight, mode of delivery and perinatal mortality rate in twin births ○ Spontaneous delivery; ● vaginal breech delivery; □ forceps; ■ caesarean section

Table 7.8. Fetal outcome by birthweight and booking status in twin births in hospital

Birthweight (kg)	Live*		IUD before admission		IUD after admission		Neonatal deaths		All births	
	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked
<1·00	0	0	10	7	7	2	11	20	28	29
1·00–2·00	90	72	33	4	13	3	50	40	186	119
2·01–2·50	131	198	18	2	7	3	6	8	162	211
2·51–3·00	82	189	12	2	7	1	2	7	103	199
3·01–3·25	12	61	2	0	1	1	1	0	16	62
3·26–3·50	6	25	3	0	0	1	0	0	9	26
3 51–4·00	1	18	0	0	0	0	0	0	1	18
≥4 01	0	1	0	0	0	0	0	0	0	1
Total	322	564	78	15	35	11	70	75	505	665
Not recorded	5	5	3	1	1	1	4	0	13	7
Percentage with low birthweight (≤2·5 kg)	69%	48%	78%	87%	77%	73%	96%	91%	74%	54%

* Alive when discharged from hospital
IUD, Intrauterine death

second twin was probably retained for ≥12 h before the affected patient reported to hospital.

Where the second twin was retained during twin delivery in hospital, the cause of the delay was cephalopelvic disproportion associated with the second baby on two occasions, and compound presentation on one occasion. All three were delivered by caesarean section. Spontaneous delivery occurred twice and vaginal breech three times. Afterwards one had a postpartum haemorrhage, and blood transfusion was required in three women. There were six live babies, one stillbirth and one early neonatal death. The mean birthweight of seven of the eight babies was 2·5 kg.

The retained second twin, where the first twin was born outside hospital, presented far more formidable problems. To begin with only 14 out of the 116 had had any antenatal care. Malpresentations present were breech (23), transverse lie (19), face or brow (2) and occipitoposterior position (1). As well as these malpresentations, the frequencies of other complications were anaemia in 13, pre-eclampsia in 11, uterine rupture in four, cord prolapse in two and antepartum haemorhage in one. With the frequency of fetal malpresentation as high as 39%, not surprisingly the operative delivery rate was also high (45%), these were vaginal breech delivery (33), forceps (4), caesarean section (5), embryotomy (9), and laparotomy for uterine rupture (4).

Of the 116 babies, only 71 survived; 32 died *in utero,* 26 before admission, 11 were neonatal deaths, and fetal outcome was not recorded in two The mean birthweight of 115 of the 116 babies was 2·32 kg (SD 0·58).

Table 7.9 shows the appalling outcome for the retained second twins compared with the second twins born within 1 h of the birth of the first twin. The proportions of low-birthweight babies in the retained (61%) and in the non-retained (62%) second twin were comparable. The important differences were in the proportions of women needing operative deliveries often to save maternal rather than fetal lives.

Maternal deaths

The combination of problems in the 15 maternal deaths are shown in Table 7.10. Virtually all these problems were avoidable. The maternal mortality rate in twin pregnancies was 37 per 1000 in the emergency admissions and 3 per 1000 in the booked women.

Table 7.9. Mode of delivery and fetal outcome in retained and non-retained second twins

	Non-retained second twin (*n* = 622)	Retained second twin (*n* = 124)
Mode of delivery		
Spontaneous	60·0	51·6
Vaginal breach	29·7	29·0
Forceps	1 9	3·2
Caesarean section	6·3	7 3
Embryotomy	1·1	6·5
Other	1·0	2·4
Fetal outcome		
Live	75·7	63 6
IUD on admission	6·7	20·7
IUD after admission	4·4	5·8
Neonatal death	13·2	9·9
Cord prolapse	1·3	1 6

Results are percentages
IUD, Intrauterine death.

Conjoined twins

There were three pairs of conjoined twins. The first woman was booked, aged 20 years, para 1+0, educated, a non-Hausa–Fulani Nigerian and 1·57 m tall. She had had a normal twin pregnancy and had an easy spontaneous vaginal delivery at term assisted by episiotomy. The birth was followed by postpartum haemorrhage. The twin fetuses, both stillborn females, had separate heads, limbs and pelvis, but were joined ventrally from the level of the sternum, to the umbilicus. Together they weighed 5·0 kg.

The second woman in the series was a 32-year-old Hausa–Fulani, para 3+0, height 1·59 m, unbooked and illiterate. She was seen for the first time in the second stage of labour, with unmistakeable signs of uterine rupture. Delivery on 13 September 1978 was by laparotomy followed by hysterectomy The monster, already dead, was lying free in the peritoneal cavity; it had one trunk, a pair of upper limbs, a pair of lower limbs, one pelvis, and one set of female external genitalia. But there were two separate heads and two necks, although the latter were fused together side by side. It weighed 3·4 kg

The third woman was unbooked, Hausa, illiterate, aged 28 years, para 1+0, with a haematocrit of 0·26 on admission in the second stage of labour. Fetal presentation was cephalic and easy spontaneous delivery took place. The combined

Table 7.10. Details of maternal deaths in twin pregnancy

Number	Age (years)	Parity	Interval between admission and death (h)	Complications
1	35	10	7–24	BBA twin 1, retained twin 2, placental abruption, PPH
2	26	5	7–24	Severe anaemia in pregnancy
3	35	10	7–24	BBA twin 1, retained twin 2, tetanus
4	25	6	<1	BBA twin 1, retained placenta, PPH
5	21	Not recorded	1–6	BBA twin 1, retained twin 2, breech extraction, PPH
6	27	2	1–6	BBA both twins, PPH
7*	20	2	240	Eclampsia, placental abruption, PPH, anaemia in puerperium
8	30	7	7–24	BBA twin 1, retained twin 2, uterine rupture, anaemia, laparotomy and repair of uterus
9	32	7	7–24	Anaemia, cardiac failure, prolonged labour, retained placenta, PPH
10	30	0	192	BBA, anaemia, retained placenta, genital sepsis
11	30	6	1–6	BBA, postpartum hypertension, anaemia
12	35	10	24–168	Pre-eclampsia, caesarean section, anaemia in puerperium
13	18	1	192	Eclampsia, caesarean section, puerperal anaemia and genital sepsis
14	29	6	<1	BBA, severe anaemia
15	16	1	7–24	Eclampsia

* This was the only booked patient, the others were unbooked emergency admissions
BBA, Born before arrival, PPH, postpartum haemorrhage.

weight of the stillborn males was 3·9 kg, with one rather large head, and two trunks one being parasitic on the other

Triplet pregnancy

Sixteen women had a triplet pregnancy, 12 were Hausa–Fulanis (10 unbooked, 12 illiterate) and four were other Nigerians (all booked and one educated). Age and parity distributions are shown in Appendix 7 1

None of the six booked women was free from antenatal complications yet none was admitted to hospital during pregnancy. The complications were mild anaemia (3), hydramnios (1), pre-eclampsia (2), eclampsia (1) and APH unclassified (1). All deliveries were straightforward. Two women gave birth to all three babies spontaneously In two others, an easy spontaneous birth of the first baby was followed by assisted breech delivery of either one or both of the other two babies. In the remaining two women, the sequence of deliveries was vaginal breech delivery for the first baby and rapid and spontaneous delivery for the other two babies. Postpartum haemorrhage and puerperal hypertension were additional complications. One woman was sterilized by tubal ligation, and in her case, all four children from previous pregnancies and two of the three triplet babies were alive.

The 10 unbooked women were first seen either after delivery at home (one woman who eventually died) or during the first stage of labour (2), in the second stage (5) and in the third stage (2). The problems during labour, including prolonged labour (1), postpartum haemorrhage (4), retained placenta and manual removal of placenta (2), were associated with anaemia in one patient and diarrhoea in another. Modes of delivery were as follows: spontaneous delivery of all three babies in four women, spontaneous delivery of the first followed by vaginal breech delivery of either one or both of the remaining two babies in five women. The only woman to require instrumental delivery had an easy forceps delivery of the second baby, the other two babies being easy spontaneous deliveries. In the puerperium, anaemia (1) and genital sepsis (2) were the only complications.

One of the unbooked women aged 30 years

para 6+0 died from the combined effect of postpartum haemorrhage, retained placenta and genital sepsis, having had a home delivery before admission to hospital.

The perinatal mortality rates were 277 per 1000 (five out of 18) in the booked women and 500 per 1000 (15 out of 30) in the unbooked women. Of the 20 perinatal deaths, five occurred at home (four stillbirths and one neonatal death) and 15 in hospital (five stillbirths and 10 neonatal deaths). The mean birthweight was 1·775 kg (SD 0·40) range 1·10–2·35 for 18 babies born in the booked group compared with 1·663 kg (SD 0·39) for the 23 babies born in the unbooked group that were weighed at birth. Twenty-nine babies were male and 19 female.

As a group, these women with a triplet pregnancy were quite tall with an average height of 1·60 m compared with 1·57 m for the women in the survey as a whole.

Quadruplet pregnancy

The two women who bore quadruplets were both illiterate, of Islamic faith, Hausa–Fulanis, in their 30s with four and five previous births respectively. All children from their previous pregnancies were alive. The one woman whose height was measured was 1·55 m tall. Both were unbooked and were first seen in the first stage of labour. At that time, the haematocrit, measured in one of them, was 0·34 and she also had mild pre-eclampsia. One set of quadruplets were all born spontaneously, their birthweights being 1·70, 1·50, 1·40 and 1·50 kg. The first two babies survived, the third and fourth were early neonatal deaths from infection. Of the babies in the other set of quadruplets, the second, third and fourth were all easy vaginal breech deliveries, following a spontaneous delivery of the first. Their birthweights were 1·15, 1·25, 1·10 and 1·25 kg, and all were early neonatal deaths from prematurity. All eight babies were female.

Discussion

In presenting these results on multiple births, the aim has been to obtain both epidemiological and clinical information. For epidemiological purposes, the data on the booked women can be taken as a reasonable representation of the population. The relation between the frequencies of twin and triplet pregnancies in the booked followed the pattern expected in population based studies (Table 7.1). This was clearly not the case for the emergency admissions where the twinning rate was high and the triplet and quadruplet pregnancy rates were very high, a change which reflects the fact that many come to hospital only because of the complications associated with their multiple pregnancy.

In Zaria, women who reported for antenatal care were entirely self-selected and the majority were seen at a stage in pregnancy when they were quite well, and if they had multiple pregnancy, its presence was not evident at the time. By contrast, the women admitted as an emergency usually came to hospital for the first time when complications had not only developed but had reached an advanced stage. Furthermore, the number of unbooked women who came to hospital for care depended on such factors as ease of access to hospital and the attitude of a particular ethnic group towards hospital care. It is clear that women admitted as an emergency with twin pregnancy are a highly selected sample from an unknown population.

Most of the findings here are in keeping with existing knowledge of the epidemiology of multiple pregnancy. Principal among them is the fact that increasing maternal age and parity are both associated with rising twinning rate, especially of dizygotic pairs. For the small group of non-Nigerians in Zaria, most of whom were Europeans, Asians and blacks from other African countries, the fact that their twinning rate was much lower than the twinning rate in the booked Nigerians is in line with established data; it supports the well-described finding that when compared with other racial and ethnic groups, Nigerians have one of the highest twinning rates (Nylander 1983).

The incidence of multiple pregnancy is apparently related not only to maternal age and parity but also to maternal nutrition. According to Nylander (1983), quoting Bulmer (1958), multiple pregnancy rates fall during periods of undernutrition and socioeconomic hardship, and the rates rise when nutritional standards improve. Indirect evidence indicates such a relation between maternal nutrition and multiple pregnancy rate. The first indication is the rise in twinning rate with increasing maternal height demonstrated earlier in Aberdeen (Anderson 1956) and now confirmed in this Zaria study, but how much of this relation is due to an age–parity effect and how much is due to superior nutrition is difficult to say. The second indication is the characteristic of those of the Zaria women who had triplet and quadruplet pregnancies. Compared to the population in Zaria, the women with triplet and quadruplet pregnancies were quite tall, and their child survival rates from previous births were good. Of the 16 women who had triplets, 12 had complete data on child survival from previous births and 80% of the 44 children born to them previously were alive. The two women who had quadruplets had nine children from previous births and all were alive. This is to be compared with the rate of 70% in the unbooked group as a whole. It is probable that the women who had achieved a good rate of child survival from previous births were able to do so because they enjoyed a better standard of living and because they were capable of taking better care of themselves and their children.

A remarkable feature of this report on multiple births is the record of the birth of three sets of conjoined twins all born in the same hospital within only 14 months, March 1978 to May 1979, during which there was a total of 9244 births. Similar clusters of conjoined twins have been reported from Cape Town between February and June 1974 (Bhettay *et al.* 1975) and from Jerusalem between December 1979 and October 1981 (Kaplan & Eidelman 1983). The cause of this curious phenomenon remains a mystery. Since 1938, there have been 12 other reported sets of conjoined twin births in West Africa (Mabogunje & Lawrie 1980). Four of these 12 were from Northern Nigeria. Easy vaginal delivery frequently occurred, partly due to the fact that intrauterine fetal death and low birthweight were common. Most were females, some were liveborn, a few were surgically separated. The longest survivor, after surgical separation undertaken in London (Aird 1954), is a Nigerian woman, now a trained nurse and midwife at Zaria, and in her early thirties.

The outcome of the twin pregnancies in women who received antenatal care contrasted sharply with that in women who were admitted as an emergency. Those who do not receive antenatal care are not protected against malaria, they do not receive iron and folic acid supplements and they often prefer home to hospital delivery. The consequences of this state of affairs were predictable. Severe anaemia developed, fetal malpresentations involving the second twin went unrecognized, postpartum haemorrhage and retained placenta were frequent causes of trouble and there was no means of combating their effects during home deliveries. Operative intervention, whether to effect delivery or to arrest haemorrhage, had to be resorted to fairly often in patients many of whom were already poor operative risks. The poor fetal outcome in the emergency admissions was equally striking. Low fetal birthweight, the high operative delivery rate and the effects of the underlying maternal diseases, such as eclampsia and antepartum haemorrhage, all combined to worsen fetal prognosis.

The phenomenon of retained second twin while not peculiar to Zaria, was certainly very prevalent; 17% of all second twins were retained. In 93% of these 124 patients the matching first twin was not born in hospital but at home. In this Zaria series, the main factors associated with retention of the second twin were not the inexpert use of oxytoxic drugs, nor fetal congenital defects, nor malformations of the genital tract (Adeleye 1972), nor even conjoined twins, but the main cause of the retained second twin was obviously mechanical: the neglect of such problems as disproportion and fetal malpresentations especially transverse lie.

Appendix 7.1. Number of multiple pregnancies by maternal age and parity in the total survey population

	Maternal age (years)																	
	≤19			20–24			25–29			≥30			Not recorded			Total		
Parity	Tw	Tr	Ou	Tw	Tr	Qu	Tw	Tr	Qu	Tw	Tr	Qu	Tw	Tr	Qu	Tw	Tr	Qu
0	42	1	0	24	0	0	7	0	0	5	0	0	3	0	0	81	1	0
1	25	0	0	39	0	0	20 (1)	0	0	2	0	0	3	0	0	89 (1)	0	0
2	12	0	0	43	2	0	40	4	0	19	0	0	9	0	0	123	6	0
3	2	0	0	34	0	0	52 (1)	0	0	25 (1)	1	0	9	0	0	122 (2)	1	0
4	0	0	0	20	2	0	44	0	0	23	1	1	7	0	0	94	3	1
5	1	0	0	5	0	0	32	1	0	28	0	1	4	0	0	70	1	1
6	0	0	0	1	0	0	15	0	0	30	1	0	9	0	0	55	1	0
7	0	0	0	1	0	0	9	0	0	26	2	0	5	0	0	41	2	0
8	0	0	0	1	0	0	5	0	0	18	1	0	2	0	0	26	1	0
9	0	0	0	—	—	—	2	0	0	14	0	0	1	0	0	17	0	0
≥10	0	0	0	—	—	—	2	0	0	17	0	0	2	0	0	21	0	0
Not recorded	0	0	0	4	0	0	1	0	0	3	0	0	2	0	0	10	0	0
Total	82	1	0	172	4	0	229 (2)	5	0	210 (1)	6	2	56	0	0	749 (3)	16	2

Numbers of conjoined twins are shown in parentheses.
Tw, Twins; Tr, triplets; Qu, quadruplets.

Appendix 7.2. Twinning rate by maternal age and parity in booked Nigerian women

Maternal age (years)	Twinning rate/1000 deliveries in parity groups								
	0	1	2	3	4	5	6	≥7	Total
<15	0	0	0	—	—	—	—	—	0
	(186)	(4)	(1)						(191)
15	9 48	21·7	0	—	—	—	—	—	10·6
	(422)	(46)	(2)						(470)
16	8·81	0·0	0	0	—	—	—	—	7·4
	(454)	(75)	(10)	(1)					(540)
17–19	8·16	16·0	8·3	21 7	0	0	—	—	11·1
	(1226)	(811)	(240)	(46)	(8)	(1)			(2332)
20–24	13·0	20·6	16 8	28·0	40 0	24·1	0	0	20·1
	(922)	(1410)	(1369)	(750)	(250)	(83)	(23)	(8)	(4815)
25–29	24·8	27·6	38·9	43·3	28·2	27·4	27·5	33·0	31·6
	(202)	(471)	(771)	(961)	(779)	(402)	(182)	(91)	(3859)
≥30	25·6	0	39·8	42·2	24·0	38·7	50 6	38·0	36 6
	(39)	(73)	(201)	(308)	(458)	(439)	(336)	(552)	(2406)
Total	10·4	19·4	24·3	32·9	28·8	32·4	40·7	36·9	23·4
	(3451)	(2890)	(2594)	(2066)	(1495)	(925)	(541)	(651)	(14 613)

Total numbers of women are shown in parentheses.

Appendix 7.3. Mode of delivery and fetal complications by birth order and booking status

Characteristic	Unbooked group		Booked group	
	Twin 1	Twin 2	Twin 1	Twin 2
No of babies	376	376	353	353
Fetal complications				
Fetal distress	1 (0·3)	2 (0·3)	0	0
Retained second twin	0	105 (27·9)	0	16 (4·5)
Presentation				
Cephalic	329 (87·5)	267 (71 0)	285 (80 7)	241 (68·3)
Breech	39 (10·4)	81 (21·5)	57 (16·1)	94 (26·6)
Occipitoposterior	2 (0·5)	2 (0·5)	2 (0·6)	4 (1·1)
Face or brow	0	2 (0·5)	0	1 (0·3)
Transverse	4 (1·1)	24 (6·4)	5 (1 4)	13 (3·7)
Not stated	2 (0·5)	0	4 (1·1)	0
Cord prolapse	2 (0·5)	4 (1·1)	4 (1·1)	6 (1 7)
Mode of delivery				
Spontaneous	302 (80·3)	219 (58·2)	258 (73·1)	204 (57·8)
Vaginal breech	41 (10·9)	104 (27·7)	70 (19·8)	116 (32·9)
Forceps	6 (1·6)	6 (1 6)	9 (2 5)	10 (2·8)
Caesarean section	21 (5·6)	29 (7·7)	16 (4·5)	18 (5·1)
Embryotomy	4 (1·1)	11 (2 9)	0	4 (1·1)
Other	2 (0·5)	7 (1·9)	0	1 (0·3)
Fetal outcome				
Live	289 (76·9)	244 (64·9)	305 (86·4)	294 (83·3)
IUD on admission	28 (7·4)	54 (14·4)	4 (1·1)	12 (3·4)
IUD after admission	9 (2·4)	27 (7·2)	6 (1·7)	6 (1·7)
Neonatal death	50 (13·3)	51 (13·6)	38 (10·8)	41 (11 6)
Congenital defects				
Minor	4 (1·1)	3 (0·8)	3 (0·8)	3 (0·8)
Major	2 (0·5)	2 (0·5)	4 (1·1)	8 (2·3)

Results are number of babies with percentages in parentheses.
IUD, Intrauterine death

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8. Mode of delivery with notes on rupture of the gravid uterus and vesicovaginal fistula

Summary. Among singleton births in hospital, the operative delivery rates were 10% in the 14 225 booked women and 31% in the 5803 unbooked women. The various operative delivery rates were vaginal breech 1·6%, forceps 1·7%, caesarean section 6·4%, embryotomy 0·1% and other deliveries 0·1% in the booked group compared with vaginal breech 2·6%, forceps 4·6%, caesarean section 18·2%, embryotomy 3·7% and other deliveries 2·3% in the unbooked group. Neglected obstructed labour was the dominant problem and resulted in uterine rupture in 203 patients and vesicovaginal fistula (VVF) in 79. In this respect, the Hausa–Fulani, the unbooked, the illiterate, those of Islamic faith, and those resident outside Zaria were the most vulnerable. The mean fetal birthweight in women who developed VVF after obstructed labour was 2·77 kg for the few surviving babies and 3·14 kg for the perinatal deaths. Fetal loss associated with vaginal breech delivery was 26% compared with 8% for breech presentations born by caesarean section.

Labour is a horrifying experience for a substantial proportion of women in Northern Nigeria, as it is in many other places in the Third World (Rao 1975; Zake 1982; Karan *et al.*, 1983; Ityavyar 1984). This report, confined chiefly to singleton births in hospital, examines the various modes of delivery, in terms of the surrounding circumstances and fetal outcome, especially in the women who had not received antenatal care. The opportunity is taken to make observations on the 203 women with rupture of the uterus and 79 with vesicovaginal fistula (VVF).

Social factors

Appendix 8 1 shows the relation between the mode of delivery and various important social characteristics of the women; Table 8.1 sets out the modes of delivery in the booked and the unbooked women excluding 42 women whose booking status was not stated. The contrast between the Hausa–Fulani and the other Nigerians (Appendix 8.1) and between the booked and unbooked groups (Table 8.1) was very sharp. The booked women rarely had embryotomy and 'other deliveries', and the operative delivery rate among them was a third of the rate in the unbooked group. For this and other reasons, the booked and the unbooked groups will be considered separately.

Booked women

General observations

By virtue of the fact that the booked women had all received antenatal care, over 70% of them were healthy when they reached the end of pregnancy. Of those who were not, some had chronic ailments such as valvular heart disease and peripartal cardiac failure (27 women), HbSS (22), HbSC (6) and diabetes mellitus (8). There were 25 with uterine fibroids and ovarian tumours, 12 with bone and joint disease, chiefly deformities from old poliomyelitis, but none with rickets or osteomalacia, Common conditions such as anaemia (763 women) and infective diseases (268), seen at booking or shortly afterwards, were treated before the onset of labour. Furthermore, in most of those with disproportion, trouble was foreseen and the mode of delivery was planned well in advance of the onset of labour.

The frequencies of the various complications

Table 8.1. Mode of delivery by booking status in singleton births in hospital

	Booked group			Unbooked group		
Mode of delivery	No	% of group	% of total group	No.	% of group	% of total group
Spontaneous delivery	12 805	90·0	63·9	3977	68·5	19·9
Vaginal breech	232	1·6	1·2	153	2·6	0·8
Forceps	239	1·7	1·2	265	4·6	1·3
Caesarean section	912	6·4	4·6	1055	18·2	5·3
Embryotomy	17	0·1	0·1	217	3·7	1·1
Other deliveries	20	0·1	0·1	136	2·3	0·7

Table 8.2. Fetal outcome by mode of delivery, and booking status in singleton births in hospital

	Fetal outcome				
Mode of delivery	Live	IUD on admission	IUD after admission	Neonatal death	% Perinatal death
Booked group					
Spontaneous delivery	12 500	118	65	122	2·4
Vaginal breech	163	26	16	27	29·7
Forceps	216	3	3	17	9·6
Caesarean section	848	8	11	45	7·0
Embryotomy	0	11	6	0	—
Other deliveries	7	9	4	0	65·0
Unbooked group					
Spontaneous delivery	3308	363	100	206	16·8
Vaginal breech	56	62	19	16	63·4
Forceps	191	28	7	39	27·9
Caesarean section	816	57	46	136	22·7
Embryotomy	0	204	13	0	—
Other deliveries	12	105	10	9	91·2

IUD, Intrauterine death

present in labour were: pre-eclampsia (5·8%), previous caesarean sections (4·7%), disproportion (4·0%), other previous operations (2·1%), prolonged labour (1·8%), eclampsia (0·9%), hypertension (0·7%), placenta praevia (0·5%), placental abruption (0·3%), antepartum haemorrhage (unclassified) (0·3%), fetal distress (0·6%). The induction rate was 2·0%.

Of those admitted in labour, 7·1% were in the second stage, but the proportion varied according to the eventual mode of delivery: it was 7·4% for spontaneous delivery, 8·6% for vaginal breech, 5·4% for forceps and 2·5% for caesarean section.

After delivery, there was retained placenta in 0·4% of spontaneous deliveries, in 1·3% of vaginal breech deliveries and none in forceps deliveries. Postpartum haemorrhage (PPH) occurred in 1·4% of spontaneous deliveries, 3·9% of vaginal breech and 7·1% of forceps deliveries.

In total, 11·5% required episiotomy and only 4% needed blood transfusion, most of them after abdominal deliveries.

Fetal outcome

The relation between fetal outcome and mode of delivery is shown in Table 8.2. Fetal loss was under 10% in spontaneous and forceps deliveries and in caesarean sections, but it was just under 30% in vaginal breech deliveries.

Table 8.3. Prevalence of low birthweight (≤2·5 kg) by booking status, mode of delivery and fetal outcome, in singleton births in hospital

	Prevalence of low birthweight (%)							
	Live		IUD on admission		IUD after admission		Neonatal death	
Mode of delivery	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked	Booked	Unbooked
Spontaneous delivery	7	19	46	56	41	50	58	68
Vaginal breech	14	21	62	44	21	58	52	67
Forceps	6	22	67	37	33	71	29	34
Caesarean section	7	12	63	26	36	28	33	23
Embryotomy	—	—	44	16	17	47	—	—
Other deliveries	0	0	33	17	0	13	—	50

IUD, Intrauterine death

Birthweight

Table 8.3 shows the proportion of low-birthweight babies associated with the various modes of delivery. As expected, live births were heavier than the perinatal deaths, and among the live-births the proportions of low-birthweight babies born spontaneously, by forceps or by caesarean section were all comparable and under 10%. Babies who died *in utero* before admission and who were subsequently born by the breech, forceps delivery and caesarean section were particularly light, and this was associated chiefly with antepartum haemorrhage (APH).

Mode of delivery and fetal outcome in breech presentations

Table 8.4 compares the fetal outcomes in singleton breech presentations born vaginally with those born by caesarean section in hospital. The data exclude those with the following complications: eclampsia, placenta praevia, placental abruption, previous caesarean section, other previous operations and haemoglobinopathies. Breech extraction as opposed to assisted vaginal breech delivery was performed only once.

Fetal loss associated with vaginal breech delivery was three times as high as it was with breech delivered by caesarean section.

In terms of the distribution of maternal age and parity and the prevalence of low birthweight, those delivered vaginally and those sectioned were comparable. The difference was in their height distributions and in the prevalence of contracted pelvis. In the following height groups: ≤1·50 m, 1·51–1·54 m, 1·55–1·59 m, 1·60–1·64 m and ≥1·65 m, the proportions of those women who had a vaginal breech delivery were 4·3%, 22·0%, 37·2%, 24·4% and 12·2% respectively compared with 20·0%, 31·4%, 28·6%, 14·3% and 5·7% of those delivered by caesarean section ($\chi^2 = 13{\cdot}89$, d.f. = 4, $P > 0{\cdot}01$). Pelvic contraction was present in over 90% of breech presentations delivered by caesarean section compared with under 10% in those delivered vaginally.

Table 8.4. Fetal outcome in breech presentations by mode of delivery in the booked women

	Mode of delivery in breech presentation	
Fetal outcome	Vaginal	Caesarean section
Live	128	33
IUD on admission	13	0
IUD after admission	11	1
Neonatal death	21	2
Total	173	36
Low birthweight (%)	19·7	16·7
Perinatal deaths (%)	26·0	8·3

Results are numbers of babies or percentages as appropriate
IUD, Intrauterine death.

Unbooked women

General considerations

Over 70% arrived at hospital because difficulties had developed during labour or because a pre-existing problem, such as anaemia, had become apparent for the first time during labour at home. The frequencies of the commonest labour complications were disproportion (18·1%), prolonged labour (15·8%), retained placenta (12%), eclampsia (5·5%), pre-eclampsia (7·5%), placenta praevia (3·0%), uterine rupture (2·6%), placental abruption (2·5%), APH from a gishiri cut (0·9%), APH from other causes (2·0%) and cord prolapse (1·2%).

As well as these obstetric complications, other associated diseases present included anaemia (9·1%) and bacterial infections particularly urinary infections (0·3%). There were six women with meningitis, six with hepatitis and eight with severe gastroenteritis. Anaemia untreated during pregnancy was often aggravated by obstetric haemorrhage, so much so that in 30% of women who were anaemic in labour, the haematocrit was <0·19.

Of the unbooked women 23·7% were in the second or third stage of labour when they were admitted as an emergency.

Table 8.1 shows that 31% of the unbooked women required operative delivery. Indeed the unbooked women delivered by caesarean section, embryotomy and 'other deliveries' comprised 7% of all deliveries in the survey population.

Fetal outcome

In the emergency admissions, 14% of the babies had died *in utero* even before admission and 33% of intrauterine deaths were associated with obstructed labour and required embryotomy or 'other delivery'. The fetal loss associated with spontaneous delivery and caesarean section was <25%, but it was nearly 30% with forceps delivery and over 60% with vaginal breech delivery.

Birthweight

Live births resulting from all deliveries, 'other deliveries' and perinatal deaths associated with embryotomy had the lowest proportion (<23%) of low-birthweight babies (Table 8.3) and the neonatal deaths following spontaneous delivery and vaginal breech delivery had the highest.

Spontaneous delivery

Anaemia. pre-eclampsia, eclampsia, APH, all common in this group (see chapter 11) often led to low birthweight and to intrauterine death even before admission. With the babies already dead *in utero* and in the absence of disproportion, because the babies were often light, it made sense to allow spontaneous delivery whenever the maternal condition permitted it.

Vaginal breech delivery

Poor fetal survival, which characterized this group, resulted from at least three factors. In 41% of the vaginal breech deliveries, the fetus was dead on admission; 44% were of low birthweight and 27% of the women arrived in the second stage of labour, in some with the breech already outside the vulva and the fetal head undelivered.

Forceps delivery

In the women admitted as an emergency, forceps delivery was often used, not so much to shorten the second stage of labour in the presence of maternal disease, but to terminate labour which had already been unduly prolonged even before admission. In this group 19% arrived at hospital in the second stage of labour, and the delay was associated with occipitoposterior position of the fetal head in 16%, with mild to moderate disproportion in 11%, with pre-eclampsia in 16% and with eclampsia in 39%. Kielland's forceps rotation and delivery was required in just over a third. Postpartum haemorrhage occurred in 9% after forceps delivery.

Caesarean section

Just under one in five of all the unbooked women were delivered by caesarean section chiefly because of obstructed labour due to disproportion, which was present in 69%. The frequencies of other complications were prolonged labour (38%), eclampsia (12%), placenta praevia (18%). transverse lie of the fetus (3%), breech presentation (4%), brow and face presentation (2%), pre-eclampsia (11%).

Of the unbooked patients who were delivered by caesarean section, 157 arrived in the second stage of labour with major obstruction. All the features of prolonged obstruction described by Lawson (1967) and by Philpott (1982*b*) were seen during caesarean section such as the impaction of the fetal head in the bony pelvic cavity, gross moulding of the fetal skull and enormous caput succeedaneum often visible at the introitus even though the fetal skull was arrested at the pelvic brim. The women had ketoacidosis, dehydration, vulval oedema, urethral compression, bladder oedema and distension, heavily blood-stained urine, thinning and bruising of the lower uterine segment, intra-uterine infection with thick offensive heavily meconium-stained amniotic fluid, and severe haemorrhage later at the operation. In addition, in Zaria patients, small-bowel dilatation, oedema of the broad ligament and ascites were also observed. In these circumstances caesarean section required technical modifications described previously (Harrison 1985).

To ensure the best possible exposure, a sub-umbilical vertical incision was preferred to transverse suprapubic incision in opening the abdomen. When urethral catheterization was rendered impossible, as it often was when the urethra was compressed by the presenting fetal head, the bladder was emptied by needle aspiration after the abdomen had been opened but before the lower uterine segment was exposed. Where the fetal head was firmly wedged at the pelvic inlet, and with gross moulding and large caput present, disimpaction per abdomen by a hand through the transverse lower segment incision was sometimes impossible. In such cases, an assistant had to disimpact the fetal head per vaginam. The resulting trauma to the babies partly explains the large number of neonatal deaths associated with caesarean sections in the unbooked group (Tables 8.2 and 8.3).

Control of haemorrhage from the bruised and torn lower uterine segment, from the vessels in the broad ligament and sometimes from tears in the vaginal vault was another problem. When conventional measures failed to secure haemostasis, this was eventually achieved by ligation of the internal iliac artery in one primigravidae and by hysterectomy in two parous mothers. All three women, so treated, survived.

Embryotomy

There were 173 craniotomies and 32 decapitations in the emergency admissions compared with 15 craniotomies and one decapitation in the booked group. The techniques used were those described by Lawson (1982) except that Queen Charlotte's embryotomy scissors, not the Blond-Heidler saw, were used to sever the fetal neck. Of the women delivered by embryotomy, 71% were already in the second stage of labour on admission and in 94% the baby was already dead *in utero*. There were other problems. Even after the fetal skull had been perforated and the head severed, delivery was still difficult in some because of the extreme degree of pelvic contraction, especially in early teenage primigravidae.

After the relief of the obstruction by embryotomy or by any other operation, the bladder was drained continuously for 6 days to improve the chances of spontaneous healing of bladder injuries. Only 18% of the babies were of low birthweight and 41% weighed between 3·01 and 4·2 kg.

'Other deliveries'

The diagnoses made and the nature of the modes of delivery in this group are shown in Table 8.5. The management of uterine rupture was the commonest problem (see below). Where Braxton Hicks bipolar podalic version was employed in the management of placenta praevia, this was because the fetus was either dead *in utero* or very small, and the poor general condition of the woman militated against caesarean section. Even so, cervical laceration was found afterwards in two of the five women; repair per vaginam was successful. In two women with suspected uterine rupture, the uterus was found to be intact at laparotomy and the abdomen was closed. Subsequently spontaneous delivery occurred in one woman; the other had an assisted breech delivery, in the course of which the aftercoming head was perforated to overcome disproportion. The two other cases of assisted vaginal delivery—complicated by constriction rings and shoulder dystocia—required very forceful vaginal delivery.

Not shown in Table 8.5, because the birth of the baby took place at home, was a bizarre case of uterine rupture, which presented as retained placenta. Spontaneous delivery had occurred at home, but the placenta had escaped into the peritoneal cavity through the rent along one of the margins of the upper uterine segment.

Dehydration and high haematocrit levels caused problems and the need for blood transfusion was exceedingly high (84%).

Blood transfusion

The proportion of women who required blood transfusion in the booked and unbooked groups

Table 8.5. Type of 'other deliveries' in unbooked singleton births in hospital

Diagnosis	Mode of delivery	No. of women
Rupture of uterus	Laparotomy, repair of ruptured uterus	92
Rupture of uterus	Laparotomy, hysterectomy	14
Suspected rupture of uterus	Laparotomy followed by spontaneous delivery	1
Suspected rupture of uterus	Laparotomy followed by breech delivery with perforation of after coming head	1
Obstructed labour	Symphysiotomy	9
Placenta praevia IUD	Braxton Hicks bipolar podalic version followed by spontaneous breech delivery	5
Hydrocephaly	Spontaneous delivery after aspiration	2
Advanced extrauterine pregnancy	Laparotomy and delivery	3
Transverse lie and IUD	Version and breech extraction of very small fetus	2
Constriction ring	Assisted vaginal delivery	1
Shoulder dystocia	Assisted vaginal delivery	1
Total		131*

* Excludes five cases which are unaccounted for
IUD, Intrauterine death.

Table 8.6. Prevalence of blood transfusions by mode of delivery and booking status in singleton births in hospital

	Number of women		Prevalence of blood transfusions (%)	
Mode of delivery	Booked	Unbooked	Booked	Unbooked
Spontaneous delivery	12 805	3977	1	9
Vaginal breech	232	153	5	16
Forceps	239	265	10	15
Caesarean section	912	1055	35	51
Embryotomy	17	217	29	41
Other deliveries	20	136	65	85
All deliveries	14 225	5803	4	20

are compared in Table 8.6 in relation to the mode of delivery. The need for blood transfusion was five times greater in the unbooked than in the booked group and it was greatest for the women having 'other deliveries' in the unbooked group. Each of those transfused received 1–12 units of blood.

Uterine rupture

Uterine rupture was associated with illiteracy, lack of antenatal care, Islamic faith, Hausa–Fulanis, residence outside Zaria, high parity and short stature. The 203 women with uterine rupture in this series were distributed as follows: 26 booked and 177 unbooked; 10 other Nigerians and 184 Hausa–Fulanis; 10 Christians and 190 women of Islamic faith; two with primary education and 201 without any formal education; 51 resident in Zaria and 152 from outside Zaria; two were aged 16 years and the remainder were aged ≥17 years; 6 were primigravidae, 22 para 1, 27 para 2, 30 para 3 and 118 para ≥4, the rates of uterine rupture in these five parity groups being 0·1%, 0·6%, 0·8%, 1·1% and 1·9% respectively. The women with ruptured uterus had a mean height of 1·53 m and 28% of them were ≤1·50 m compared with a mean height of 1·57 in the survey population of whom only 10% were ≤1·50 m.

Table 8.7 shows the aetiological factors and treatment in the 152 unbooked and 24 booked women with singleton births and with uterine rupture, who were delivered in hospital. Disproportion, prolonged labour, malpresentations and delay in reporting to hospital were all important Malpresentations were transverse fetal lie (20), breech (10), occipitoposterior position of

Table 8.7. Aetiological factors and treatment in uterine rupture by booking status (singleton births in hospital)

Aetiological factors	Unbooked group	Booked group
No. with uterine rupture	152	24
Previous caesarean section	20	10
Previous VVF repair	5	0
Other previous operation	1	1
Disproportion	87	7
Prolonged labour	79	6
Fetal malpresentations	48	4
Stage of labour on admission into hospital		
First stage	56	13
Second stage	76	4
Not stated	20	7
Treatment		
Repair + sterilization	119	16
Hysterectomy	21	2
Caesarean section + sterilization	12	6

Results are numbers of women

Table 8.8. Place and mode of delivery, by booking status in women with uterine rupture

Place of delivery and mode of delivery	Unbooked group	Booked group
Singletons in hospital		
Spontaneous delivery	3 (0)	6 (0)
Vaginal breech	6 (1)	2 (0)
Forceps	2 (0)	1 (0)
Caesarean section	12 (0)	6 (0)
Embryotomy		
Craniotomy	16 (3)	0 (0)
Decapitation	7 (0)	0 (0)
Other deliveries	106 (15)	9 (0)
All deliveries	152 (19)	24 (0)
Outside hospital		
Born before arrival		
Singletons	12 (1)	2 (0)
Twin births	5 (1)	0 (0)
Undelivered	8 (8)	0 (0)
Grand total	177 (29)	26 (0)

Results are numbers of women with number of maternal deaths shown in parentheses.

the fetal head (10), face and brow (8) in the unbooked; and breech (3) and occipitoposterior position (1) in the booked.

Table 8.8 shows the relation between mode of delivery and uterine rupture in the booked and unbooked women. The majority were unbooked with singleton births. Five of the eight who died undelivered did so within minutes of admission to hospital, and the diagnosis of uterine rupture was confirmed by vaginal examination of the body Of 43 women in whom uterine rupture was discovered after vaginal delivery in hospital, excessive vaginal bleeding in seven (five booked, two unbooked) suggested that this had happened, and uterine exploration confirmed the presence of the injury. In the remaining 36, the injury was not apparent until it was felt on routine uterine exploration either after vaginal delivery in six women with previous caesarean section (three booked, three unbooked), or after difficult instrumental vaginal delivery in 30 (one booked, 29 unbooked), mostly with embryotomy. It must be stressed that where uterine rupture was associated with embryotomy, the injury might well have been present even before delivery, but it was not apparent at that time because the presenting fetal part had acted as a plug at the site of the rupture, and in so doing, prevented haemorrhage. Indeed, were it not for this effect, those women who had travelled a long way to hospital, would have died from blood loss long before they arrived.

Eighteen women with uterine rupture were treated by caesarean section (Table 8.7). In the remainder, operative treatment was either by hysterectomy or by surgical repair and bilateral tubal ligation depending largely on the extent of the injury. Three (13%) out of 23 women died after hysterectomy and 16 (12%) out of 135 died after surgical repair and bilateral tubal ligation, Haemorrhage, peritonitis and septicaemia were the leading causes of death.

The mean birthweight of 168 singleton babies whose mothers had uterine rupture was 3·26 kg; 14% weighed ≤2·50 kg, 24% between 2·51 and 3·00 kg, 55% between 3·01 and 4·0 kg and 7% >4·9 kg.

Vesicovaginal fistula

In the survey population, 79 women had a vesicovaginal fistula (VVF), 75 of them had a VVF only, one had a rectovaginal fistula alone, and three had both combined. This excludes the hundreds of women and teenage girls with VVF seen for the first time after the puerperium (Tahzib 1983).

The most vulnerable included those who were

Table 8.9. Distribution of vesicovaginal fistula (VVF) by mode of delivery, and booking status (singleton births in hospital)

	No. of women with VVF	
Mode of delivery	Unbooked group	Booked group
Spontaneous delivery	8 (7)	2
Vaginal breech	0	0
Forceps	5 (3)	0
Caesarean section	8 (1)	0
Craniotomy	33 (6)	1
Other deliveries	8	0
All deliveries	62 (17)	3 (0)

Numbers of women with obstetric palsy are shown in parenthesis.

Table 8.10. Distribution of fetal birthweight by mode of delivery in women with vesicovaginal fistulas (singleton births only)

	Birthweight (kg)		
Mode of delivery	Mean	SD	No of babies
Spontaneous	3·07	0·58	10
Forceps	2·82	0·40	4
Caesarean section	3·35	0·34	7
Embryotomy	3·06	0·52	32
Other deliveries	3·28	0·39	7
Total	3·10	0·50	60

short, unbooked, illiterate, of Islamic faith, young Hausa–Fulanis, resident outside Zaria. Of the 79 women with VVF, 66 (65 singletons and one twin pregnancy) gave birth in hospital (Table 8.9). All 66 women were illiterate, 97% were of Islamic faith, 95% were unbooked, 94% were Hausa–Fulani, 93% lived outside Zaria, 33% were primigravidae (compared with 28% in the survey population) and 20% were aged ≤16 years (compared with 11% in the survey population). Of the women with a VVF, 30% were ≤1·50 m in height compared with 10% in the survey population.

Although 66 of the women who developed a VVF were delivered in hospital and the injury was most often associated with craniotomy (Table 8.9), in virtually every case, the damage to the bladder and vaginal walls had occurred during prolonged obstructed labour at home. In addition to the VVF, there was obstetric palsy in 17 women (all unbooked), uterine rupture in 10 (all unbooked) and nine (eight unbooked) had already had a gishiri cut at home before arrival at hospital.

Sixty of the 65 singleton babies born to women with a VVF were weighed at birth (Table 8.10). The mean birthweight was 3·10 kg (SD 0·50, range 1·80–4·45) and 13% weighed ≤2·50 kg. Of the 65 singleton births, only five (8%) survived, three after spontaneous delivery, one after forceps delivery and one after caesarean section. Forty-six fetuses were dead on admission, six died *in utero* after admission and eight were neonatal deaths. The mean birthweights of the survivors and of the perinatal deaths were 2·77 kg and 3·14 kg respectively.

Puerperium after VVF and uterine rupture

Table 8.11 compares puerperal morbidity and mortality rates in mothers who had a VVF following obstructed labour, in those with uterine rupture and in booked and unbooked women in the entire survey population The puerperium was particularly stormy in those with VVF, so much so that none among them was free from one kind of infection or another.

Of the 79 women with VVF, 12 died, three having been delivered at home before admission. Four died after craniotomy, four after abdominal delivery and repair of ruptured uterus, and one after caesarean section Death was associated with fulminating bacterial infection especially genital sepsis and wound sepsis in all cases, with haemorrhage playing some part in four of them.

Twenty-nine women died following uterine rupture, two had been delivered at home, 19 were delivered in hospital and eight died undelivered. Death was largely from the combined effects of haemorrhage, shock, peritonitis and septicaemia. The significance of maternal haematocrit level in the prognosis of these women is discussed in chapter 12

Discussion

A striking feature of this analysis is the link between antenatal care and safe childbirth, most clearly evident in the women with disproportion. This particular complication is one which develops in both booked and unbooked women, but the difference is that labour rarely obstructs in the booked, as it so often does in the emer-

Table 8.11. Prevalence of major puerperal complications (%) in relation to vesicovaginal fistula (VVF), uterine rupture and booking status

Major puerperal complications	Women with VVF	Women with uterine rupture	Unbooked group	Booked group
Secondary PPH (%)	1	1	1	0
Anaemia in puerperium (%)	34	18	13	2
Genital sepsis (%)	68	40	8	2
Wound sepsis (%)	37	12	7	3
Meningitis (*n*)	1	0	6	0
Septicaemia (%)	6	3	1	0
Other infections chiefly postoperative bronchopneumonia (%)	8	10	3	1
Blood transfusion (%)	67	84	25	4
Maternal deaths per 1000	152	143	29	1
No of days from delivery to discharge or death				
mean (SD)	19 (23)	12 (10)	5	3
range	1–145	1–56	—	—

gency admissions. During the antenatal period in the booked women, transverse fetal lie is corrected when necessary, disproportion is usually detected, and preparations are made for the most appropriate form of delivery. During labour, the booked women report early, well before labour obstructs and before intrauterine death occurs, making delivery by embryotomy unnecessary.

In the booked group, the overall fetal survival rate does not appear to be as good as it should have been. This is best illustrated by the results of vaginal breech delivery. It is true that low birthweight and intrauterine death before admission contribute towards the poor fetal outcome in these women, but there is a more fundamental issue. The hospital services in Zaria were overwhelmed by an exceedingly large proportion of emergency admissions, and their number was much more than could be reasonably catered for. In addition, a substantial proportion of these unbooked women arrived in the second or third stages of labour, at moments when major emergency operations were absolutely mandatory if they were to survive. In patients with obstructed labour where laparotomy was needed for its relief, all such operations were very time-consuming Afterwards, prolonged periods of intensive care were often needed. In this way, by diverting a substantial proportion of available resources towards the care of unbooked women, the hospital was unable to render to the booked women the optimum care and attention they were entitled to expect during labour.

The operative procedures employed in the group classified as 'other deliveries' show the extent to which caesarean section was avoided, if possible, especially when intrauterine death had already occurred. Symphysiotomy, various forms of assisted vaginal delivery shown in Table 8.5 and Braxton Hicks bipolar podalic version in the presence of placenta praevia were all alternatives to caesarean section. We were very loath to carry out caesarean sections in women in whom the fetus was dead, bearing in mind the Nigerian's strong dislike of operative delivery, especially caesarean section. If a dead baby results from caesarean section, the affected woman, if she is unsophisticated, often links her loss not to the underlying obstetric complication but to hospital delivery Strong in this belief, she distrusts hospital medicine, and there is therefore no guarantee that she will report to hospital for care in subsequent pregnancies. In this situation, the danger of scar rupture is very real. So, the avoidance of caesarean section is one way of reducing future obstetric deaths.

This is not the place to enter into the argument as to which is safer in the management of uterine rupture: hysterectomy or surgical repair of the uterus and bilateral tubal ligation However, these results from Zaria show that in assessing maternal outcomes following treatment of uterine rupture, a clear distinction must be made between the results of those who received antenatal care and those who failed to do so. Uterine rupture was not fatal on the few occasions when it occurred in women who received antenatal care whether treatment was by hysterectomy, or by repair or by caesarean section. By contrast maternal outcome was very poor in the unbooked women with uterine rupture. The death rates in those treated by repair was 14%, compared with a death rate of 33% in those treated by hysterectomy (chapter 12). If, however, the results of the booked and unbooked women are combined, then the maternal mortality rates associated with both operative procedures are the same, around 13%. Maternal prognosis in uterine rupture is influenced by a host of factors and these include the severity of the injury, the presence or absence of other complications such as sepsis and the quality of medical and nursing care. From the results presented in this chapter, the indications are that survival following the treatment of uterine rupture depends rather more on the state of maternal health and rather less on the nature of the operative treatment.

Much has been said about VVF in this and other chapters: the biosocial characteristics of the affected women, their morbidity and mortality rates, and also the horrendous fetal loss associated with this affliction have all been discussed. However, further comment about fetal birthweight in such cases is worth making. Of the babies whose mothers had a VVF, the mean birthweight of 3·10 kg is almost certainly an underestimate of what the actual mean birthweight was. Half of such babies were extracted by embryotomy (Table 8.9) and loss of fetal tissue, certainly fetal blood and skull contents was inevitable. In weighing such babies, measures taken to minimize errors from this source included one routine procedure. An infant weighing scale set aside for stillbirths only was provided in the operating theatre, and the scale was always placed beside the operator during an embryotomy. This enabled the operator to place on the scale not only the main body of the stillborn infant but also other fetal parts and the reading could be recorded on the spot. Even so, the difference in mean fetal birthweight between babies born by caesarean section and those subjected to embryotomy (Table 8.10) would suggest that the loss of fetal tissue during embryotomy was about 0·3 kg.

There is another distinctive feature of the pattern of distribution of fetal birthweight in those babies born to women who developed VVF following obstructed labour. Among them, the surviving babies were on the average lighter than the perinatal deaths, whereas the reverse was always the case in all other groups of babies throughout the survey population. These differences in fetal birthweight would tend to indicate that in cases of VVF, the babies who failed to survive the perinatal period were potentially superior to those who did survive. But the number of babies is small and so firm conclusions cannot be drawn.

Lastly, in terms of maternal and fetal survival, the difference between the results following caesarean section on the one hand and the results after embryotomy and 'other deliveries' on the other hand, amply illustrate the savings there might have been, had disproportion always been relieved before labour became obstructed. The caesarean section rate would have risen but the rise would be more than compensated for by a drastic reduction in maternal mortality and morbidity (see chapter 12) and by a saving in the use of banked blood for transfusion.

Appendix 8.1. Mode of delivery, by booking status and social factors (singleton births in hospital)

Social factors	All deliveries	Spontaneous delivery	Vaginal breech	Forceps	Caesarean section	Embryotomy	Other deliveries
Booked group							
Residence							
Zaria	13 280	12 081	209	217	748	11	14
Outside Zaria	944	723	23	22	164	6	6
Ethnic group							
Hausa–Fulani	4161	3502	97	112	430	11	9
Other Nigerians	9924	9182	131	119	475	6	11
Others	111	93	3	8	7	0	0
Education							
Formal	2292	2069	22	45	153	0	3
None	11 793	10 608	208	191	753	17	16
Unbooked group							
Residence							
Zaria	2636	2063	57	106	347	37	26
Outside Zaria	3167	1914	96	159	708	180	110
Ethnic group							
Hausa–Fulani	4945	3230	142	255	986	204	128
Other Nigerians	802	696	11	9	66	13	7
Others	11	8	0	1	1	0	1
Education							
Formal	55	45	2	1	7	0	0
None	5711	3905	151	263	1041	216	135

Results are numbers of women.

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9. Pregnancy outcome following previous caesarean section, previous vesicovaginal fistula and previous surgical treatment of ectopic pregnancy

Summary. Some women in this survey population had a history of one or more surgical procedures including treatment for ectopic pregnancy (41), repair of vesicovaginal fistula (97), caesarean section (866), ectopic pregnancy and caesarean section (2) and repair of vesicovaginal fistula and caesarean section (47), leaving 21 672 who had not had any of these operations before. Pregnancy outcomes in these six groups of women were compared. The main problems were lack of antenatal care in all groups, disproportion and prolonged labour in the previous caesarean section group, urinary tract infections, an excess of low-birth-weight babies and perinatal mortality rate exceeding 140 per 1000 total births in the previous vesicovaginal fistula repair group. Rupture of the scarred uterus, always a danger, occurred in 10% of those without antenatal care and in 1·4% of those with antenatal care. Of those who had had a previous section, 45% required a further caesarean section and the overall operative delivery rate in this group was 55%

Caesarean section and obstetric fistula are two important results of obstructed labour and both may have profound influences on subsequent reproductive patterns and health. In the case of obstetric fistula, successful surgical and anatomical closure does not always cure the urinary incontinence Vaginal stenosis, often co-existing with the fistula, causes dyspareunia and prolonged periods of secondary amenorrhoea may persist after surgical repair of the fistula (Aimakhu 1974). If intrauterine synechiae is the cause, then the amenorrhoea becomes permanent and infertility results. In practice, however, the picture is not as bleak, because the affected girls are usually young and at the age when fertility is maximal so that a considerable proportion become pregnant, sometimes even before the fistula is closed.

In Northern Nigeria pelvic contraction and disproportion are both exceedingly common, and the resulting obstructed labour is often neglected. Under these circumstances, no one doubts that caesarean section has an important role to play in reducing maternal and perinatal mortality and in preventing obstructed labour The anxiety is over the safety of the operation, not only in the immediate postoperative period but also during subsequent pregnancies.

Here we examine the results of pregnancies which occur subsequent to caesarean section (CS), the surgical closure of vesicovaginal fistula (VVF), and after the treatment of ectopic pregnancy

Patients and methods

Based on whether, or not, the patient had a history of VVF repair, caesarean section or surgical treatment for ectopic pregnancy, the survey population was divided into six groups as follows (a) previous ectopic pregnancy, (b) previous CS, (c) previous VVF, (d) previous CS and previous ectopic, (e) previous VVF and previous CS and (f) none of these operations

Obstetric care after previous caesarean section and VVF repair

In the management of pregnant women with previous caesarean section, local conditions (see chapter 2) were such that the approach was conservative, and vaginal delivery was permitted whenever it was thought safe. Where there had been only one previous caesarean section, vaginal delivery was allowed so long as there was no disproportion or pelvic contraction. Both contracted pelvis and disproportion were searched for routinely at 36 weeks gestation by clinical pelvimetry, supplemented by radiological pelvimetry in some patients. Once the decision to permit vaginal delivery had been made, labour was allowed to start spontaneously and it was conducted under close supervision. As soon as the baby was born and the placenta expelled, the lower uterine segment was explored digitally for rupture or dehiscence of the lower segment scar. Those who remained undelivered after a labour of 24 h were delivered by caesarean section at that stage.

After two or more previous sections, delivery at the end of all subsequent pregnancies was by elective caesarean section. Usually, sterilization by tubal ligation was performed at the time of the third abdominal delivery.

In women with vesicovaginal fistula, care after surgical closure followed orthodox practice in that as much as possible the women were followed up to see how the repair had healed: the patients were advised to avoid coitus for 3–6 months to allow complete healing to take place at the site of vaginal surgery. The need to report early for antenatal care in all subsequent pregnancies was always stressed. For those who did, and if their homes were outside Zaria, the hospital's social services arranged temporary accommodation in Zaria. The conduct of antenatal care was otherwise routine (chapter 2).

We were aware that the size of the bony pelvis often changed markedly between the first and subsequent pregnancies in teenage Nigerian girls (chapters 5 & 6) who had not finished growing during their first pregnancies. For this reason, previous VVF repair was, by itself, not regarded as an absolute indication for elective caesarean section in subsequent pregnancies. Furthermore, in some, the fistula was from a gishiri cut performed for non-obstetric reasons (chapter 2). In these cases, if clinical and radiological pelvimetry at 36 weeks showed the pelvis suitable for vaginal delivery and there were no other contra-indications, including vaginal fibrosis and vaginal stenosis, then vaginal delivery assisted by episiotomy was permitted. Otherwise, delivery was by elective caesarean section after the 37th week of pregnancy.

Results

General considerations

The number of women in the groups were 21 672 with no previous operation, 41 with a previous ectopic, 97 with a previous VVF repair, 866 with a previous CS, two with a previous ectopic and a previous CS and 47 with a previous VVF and a previous CS. Within these groups were 260 who had had dilatation and curettage of the uterus for various reasons. Of all the women who had had previous caesarean sections, 787 had had the operation only once, 111 twice, 16 thrice and one had had the operation four times before her current pregnancy. The number of twin pregnancies was one in the previous-VVF group, 18 in the previous-CS group and one in the previous-VVF-CS group.

One of the 97 patients in the previous-VVF group was still incontinent, two attempts at surgical repair had both failed when she became pregnant.

Social characteristics

Table 9.1 shows that the previous-VVF and the previous-VVF-CS groups, made up largely of Hausa–Fulanis and Moslems, were at some disadvantage compared with the other groups. The majority lived outside Zaria, virtually all were illiterate and almost a quarter of them did not report for antenatal care despite having undergone such major operations in the recent past.

Ethnic groups

The Hausa–Fulani women were compared with other Nigerians in terms of mean age, mean parity, mean height and average number of children from previous births that were still alive (Table 9.2).

Among the Hausa–Fulanis, the parity distribution was similar in the five subgroups of previous operations, but there were obvious differences in the distribution of the other characteristics. Those with previous VVF were the youngest, they were very short, with only 30% of their children from previous births still alive compared with over 60% in the other groups.

In the other Nigerians, the previous-operations groups were similar as far as the distributions of their ages, and heights were concerned, and as with the Hausa–Fulani, the rate of child survival was least in the previous-VVF group

Table 9.1. Biosocial factors by previous operations

	Previous operations					
Biosocial factors	None	Ectopic	VVF repair	Caesarean section	Ectopic and caesarean section	VVF and caesarean section
Total no of women	21 672	41	97	866	2	47
Residence						
Zaria	77	95	23	75	100	32
Outside Zaria	23	5	77	25	0	68
Religion						
Christian	34	46	7	34	0	9
Islam	62	49	92	64	100	91
Others	1	0	0	0	0	0
Ethnic group						
Other Nigerians	50	61	11	45	0	9
Hausa–Fulani	49	37	89	54	100	91
Others	1	2	0	1	0	0
Formal Education						
Primary	6	12	1	6	0	4
Secondary	2	5	0	2	0	0
Post-secondary	2	5	1	5	0	2
None	88	78	97	86	100	94
Booking status						
Booked	66	95	78	76	100	74
Unbooked	34	5	22	24	0	26

Results are percentages
VVF, Vesicovaginal fistula

Table 9.2. Mean age, height, child survival and parity by previous operations in two ethnic groups

		Previous operations				
Maternal characteristic	All women	Ectopic	VVF repair	Caesarean section	Ectopic and caesarean section	VVF and caesarean section
Hausa–Fulani						
Mean age (years)	22·9 (11 105)	24·3 (15)	23·0 (82)	23 4 (381)	33·5 (2)	25·8 (63)
Mean height (cm)	155·4 (8011)	156·8 (14)	152·2 (71)	153·5 (343)	159·0 (2)	151·2 (32)
Mean parity	2·48 (11 659)	2·93 (15)	2·46 (86)	2·74 (392)	2·50 (2)	3·53 (36)
Mean no of living children	1·63 (10 801)	2·46 (15)	0 76 (81)	1·78 (366)	2·50 (2)	1·06 (32)
Child survival (%)	66	84	31	65	100	30
Other Nigerians						
Mean age (years)	23·9 (11 351)	28·3 (24)	23·2 (11)	25 5 (326)	—	29·3 (4)
Mean height (cm)	158·1 (10 609)	157·8 (20)	155 3 (10)	155·9 (312)	—	156·0 (4)
Mean parity	2 32 (11 584)	3·84 (25)	1·91 (11)	2·88 (334)	—	3·25 (4)
Mean no of living children	1·95 (11 193)	3·50 (24)	0 91 (11)	2·37 (308)	—	1·50 (4)
Child survival (%)	84	91	48	83	—	46

Number of observations are shown in parentheses.
VVF, Vesicovaginal fistula

Pregnancy complications

These are listed in Table 9.3. Only the differences in the prevalence of associated non-infective diseases and placenta praevia were notable. The non-infective associated disease in the previous-VVF and in the previous-VVF-CS groups was vaginal stenosis. This was from fibrosis commonly seen both before and after surgical repair in many cases of obstetric fistula in Northern Nigeria.

There was less anaemia in the previous-VVF and in the previous-CS groups, and none at all in the previous-ectopic group. This was probably because more women in these groups received antenatal care, and hence protection against anaemia than was the case in the no-previous-operation and in the previous-VVF-CS groups.

Pre-eclampsia generally thought to be rare in multiparous women was nevertheless comparatively common in the previous-CS group. The explanation would seem to be that twin pregnancy which is commonly associated with pre-eclampsia, irrespective of parity, was fairly frequent in the previous-CS group.

The increased frequency of placenta praevia in the previous-VVF-CS group was quite striking, but, of course, this group was highly parous (Table 9.2).

Of the associated infective diseases 80% were urinary tract infections, and most of the organisms cultured from urine samples were coliforms. Gastroenteritis was the other common infective disease.

Labour complications

Women with previous VVF repair with, or without, caesarean section exposed themselves to greater risks by reporting very late to hospital during labour (Table 9.4) and they, together with the previous-CS group, had the highest frequency of disproportion.

Mode of delivery

Table 9.5 shows that 1886 (9% of all singleton births) in the no-previous-operation group reported to hospital after home births compared with <4% in the previous-operations groups. Particularly striking was the fact that in the group with previous VVF with, or without, previous CS, those who came to hospital after they gave birth at home formed a very small proportion of the total number of all the births in those groups.

Among the home births, nearly 90% had had no antenatal care in the no-previous-operations group compared with nearly 40% in the previous-operations groups.

Table 9.3. Prevalence of pregnancy complications (%) by previous operations

	Previous operations					
Pregnancy complications	None	Ectopic	VVF repair	Caesarean section	Ectopic and caesarean section	VVF and caesarean section
Total no. of women	21 672	41	97	866	2	47
Anaemia	7·7	0·0	3·1	5·3	0·0	8·5
Associated infective diseases	1·7	0·0	5·2	1·7	0·0	2·1
Associated non-infective diseases	1·1	0·0	14·4	1·5	0·0	6·4
Pre-eclampsia	6·1	4·9	2·1	6·6	0·0	0·0
Hypertension	0·7	4·9	0·0	0·5	0·0	0·0
Eclampsia	2·3	0·0	0·0	1·0	0·0	0·0
Twins	3·2	0·0	1·0	2·1	0·0	2·1
APH						
Placenta praevia	1·1	0·0	2·1	2·0	0·0	8·5
Placental abruption	0·9	0·0	0·0	0·5	0·0	0·0
Other causes	1·4	0·0	0·0	1·4	0·0	2·1

Results are percentages
VVF, Vesicovaginal fistula

Table 9.4. Prevalence of labour complications (%) by previous operations

Labour complications	Previous operations None	Ectopic	VVF repair	Caesarean section	Ectopic and caesarean section	VVF and caesarean section
Number of women	21 672	41	97	866	2	47
Stage of labour on admission						
First	53·3	63 4	41·2	63 0	100	23·4
Second or third	13·4	7·3	12·4	8·7	0·0	53 2
Disproportion	6·5	2·4	16·5	23·7	0·0	10·6
Prolonged labour	5·4	2 4	6·2	5·8	0·0	0·0
Postpartum haemorrhage	2·9	2 4	1·0	2 4	0·0	0·0
Retained placenta	4·9	2·4	0·0	3 2	0·0	0·0
Uterine rupture	0·7	0·0	4·1	3·3	0·0	2·1

Results are percentages.
VVF, Vesicovaginal fistula

Table 9.5. Place of birth and mode of delivery by previous operations (singleton births only)

Mode of delivery	Previous operations None	Ectopic with or without caesarean section	VVF repair	Caesarean section	VVF and caesarean section
Hospital births					
Spontaneous	16 379	41	23	373	2
Vaginal breech	372	0	0	11	2
Forceps	484	0	0	20	1
Caesarean section	1475	1	65	391	39
Embryotomy	217	0	4	7	1
Other deliveries	133	0	3	15	1
Operative deliveries (%)	14·1	2·4	75 8	54·6	95·7
Home births*					
All	1886	1	1	32	0
% of all hospital and home births	9·0	2·3	1·0	3·8	0 0

* Born before arrival at hospital.
VVF, Vesicovaginal fistula.

Disproportion was the principal indication for operative deliveries in past and in current pregnancies. For this reason, the intergroup variations in the operative delivery rates follow closely the pattern for disproportion (Table 9.4).

Of the 866 women who had had a previous caesarean section 45% required a further section and the overall operative delivery rate was 55%.

Fetal outcome

There were 116 perinatal deaths, but we shall concentrate on the 96 which occurred in the singleton births in hospital (Table 9.6). Fetal outcome was excellent in the women with previous ectopic pregnancy with, or without, caesarean section (fetal death rate of 2·5%). In the other groups, fetal death rate varied between

Table 9.6. Place of birth and fetal outcome by previous operations

	Previous operations				
Fetal outcome	Ectopic	VVF repair	Caesarean section	Ectopic and caesarean section	VVF and caesarean section
Hospital births					
Live	39	80	743 (27)	2	39 (2)
IUD on admission	1	10	32 (1)	0	5
IUD after admission	0	1	8	0	2
Neonatal death	0	4 (1)	33 (8)	0	0
Home births*					
Live	0	1	24	0	0
Stillbirth	1	0	4	0	0
Neonatal death	0	0	4	0	0

Numbers of twin babies are shown in parentheses.
* Born before arrival at hospital.
VVF, Vesicovaginal fistula; IUD, intrauterine death.

13·4% and 15·8%. It was very noticeable that stillbirths exceeded neonatal deaths in all groups, and in 81% of the stillbirths there was already intrauterine death on admission. Under 5% of women with a previous ectopic pregnancy had failed to receive antenatal care compared with 22–26% in the other groups and this in part explains why fetal outcome was better in the previous-ectopic group

Fetal birthweight

Where fetal birthweight was recorded the proportions of babies weighing ≤2·50 kg were 13·2% in the no-previous-operation group (n = 20 070), only 7·5% in the previous-ectopic group (n = 40), 29·0% in the previous-VVF group (n = 93), 13·9% in the previous-CS group (n = 835), 15·2% in the previous-VVF-CS group (n = 46) and one of the two babies born in the previous-ectopic-CS group.

Rupture of the uterus and previous operations

None of the women with previous surgical treatment for ectopic pregnancy with, or without, caesarean section had uterine rupture Virtually all had antenatal care and the only mother judged to need abdominal delivery for disproportion was sectioned early.

Uterine rupture occurred in four (4·1%) of the previous-VVF group, in 29 (3·3%) of the previous-CS group, in one (2·1%) in the previous-VVF-CS group. These rates contrast strongly with the 160 (0·7%) women in the no-previous-operation group. Both the groups with and without uterine rupture included women who had contracted pelvis and disproportion as well as women who lived outside Zaria. Uterine rupture after a previous operation was very much associated with illiteracy, with Hausa–Fulani, and with lack of antenatal care (Table 9.7).

Under normal circumstances rupture of the uterus should rarely occur in women who have received antenatal care, but in this survey it happened in 10 women with previous caesarean section who had received antenatal care. The data were explored to discover why. Five had contracted pelvis and disproportion detected at the antenatal clinic. Elective caesarean section had been planned, but all the women defaulted, went into labour at home and failed to report until they were obviously in trouble. All five were illiterate. Of the other five, in one the injury was iatrogenic, during manual removal of the placenta for retained placenta after spontaneous delivery. In another three, uterine rupture was discovered during exploration of the uterus after uncomplicated spontaneous delivery in one, forceps delivery in one, and in the course of management of postpartum haemorrhage in one. The last woman was educated, with a good pelvis and no disproportion in

Table 9.7 Occurrences of uterine rupture by social factors and previous operations

	Previous operations							
	None		VVF repair		Caesarean section		VVF and caesarean section	
Social factor	No rupture	Rupture	No rupture	Rupture	No rupture	Rupture	No rupture	Rupture
Total no of women	21 512	160	93	4	837	29	46	1
Ethnic group								
Hausa–Fulani	10 433	144	82	4	443	26	42	1
Other Nigerians	10 884	16	11	0	386	3	4	0
Booking status								
Unbooked	7271	144	17	4	185	19	11	1
Booked	14 191	16	76	0	651	10	35	0
Education								
None	19 017	157	90	4	715	28	43	1
Educated	2308	2	2	0	112	1	3	0

VVF, Vesicovaginal fistula.

whom uterine rupture occurred in labour in our care. There were no maternal deaths in these 10 women, eight babies survived (birthweight range 2·80–4·05 kg), one was an early neonatal death (weight 2·40 kg) and another was an intrauterine death on admission (2·0 kg).

Among the unbooked women with previous operations, 24 had uterine rupture. The fact that uterine rupture had occurred was obvious on admission to the labour ward in all but three. In these three, the injury was discovered on routine exploration of the uterus after vaginal delivery, which was spontaneous in one, forceps in another and vaginal breech in the third. The woman who had a spontaneous delivery had had two previous caesarean sections yet she failed to report for antenatal care and kept away from hospital until she was clearly in difficulty. The remaining 21 women were all delivered at laparotomy, four needed caesarean section.

Fetal outcome was very poor. Seven survived (birthweight 2·65–3·20 kg) 13 were intrauterine deaths on admission (birthweight 1·25–3·10 kg), one died *in utero* after admission and the rest were neonatal deaths. There were two maternal deaths, through haemorrhage.

Maternal mortality

There were six maternal deaths (mortality rate 7 per 1000) in the women with previous operations compared with a mortality rate of 11 per 1000 in those with no previous operations. The patterns in the two groups did not differ. The causes of the six deaths were haemorrhage in four, sickle cell disease in one and acute renal failure from pyelonephritis after caesarean section in a woman with a previous VVF repair.

Fresh or recurrent vesicovaginal fistula

These occurred in two patients, one in the previous-CS group and the other in the previous-VVF group and detailed consideration of both patients is instructive.

Patient no. 1. This woman was in her second pregnancy, she was only 1·49 m in height. She had not received any antenatal care throughout her first pregnancy at the age of 15 in 1975. Labour became obstructed at her home. She then reported to our hospital, where the obstruction due to cephalopelvic disproportion was relieved by a lower segment caesarean section, and a live male infant birthweight 3·10 kg was born; her postoperative recovery was good. Her second pregnancy 3 years later followed an almost identical course to the first but this time the outcome was worse. She had not received antenatal care, labour obstructed at home, and when she finally reached hospital the baby already dead *in utero* was in advanced maceration and a vesicovaginal fistula had formed. A craniotomy was performed and a female baby birthweight 3·10 kg was extracted. The caesarean section scar was intact.

Patient no. 2. This patient was in her second pregnancy. In her first pregnancy she had a vesicovaginal fistula which resulted from an obstructed labour and spontaneous delivery at home, at the age of 14. This was successfully repaired at our hospital. Two years later, she reported for antenatal care and because there was some vaginal fibrosis, she was booked for elective caesarean section. Subsequently, she went into labour at home and reported to hospital in the second stage of labour with the baby already dead *in utero*. Spontaneous delivery took place shortly afterwards with the aid of a large episiotomy. The baby was female, stillborn, weighed 3·20 kg. Urinary incontinence was first noticed a week later.

Summary of results

Table 9.8 summarizes the main features of all the groups of women under consideration in this analysis. The disadvantages suffered by women with previous VVF with, or without, caesarean section stand out; they have the lowest rates for literacy and for child survival from previous births, and the worst fetal results in their current pregnancies. By contrast, the group of women with previous surgical treatment for ectopic pregnancy with, or without, caesarean section had quite a good reproductive performance; almost all of them had obstetric care and they had the highest literacy rate.

Discussion

One of the most important findings is that of all the women with previous VVF repair or with previous caesarean section who were treated in hospital during or after a subsequent pregnancy, more than 20% had not attended for antenatal care. They preferred instead to report for the first time when they were already at the second or third stage of labour, often with intrauterine fetal death having already taken place. The penalties were heavy and they included uterine rupture, recurrence of VVF, embryotomy, maternal and perinatal deaths. Difficulty with transport is not the only reason why so many women fail to come for antenatal care. The problem has it roots in the attitudes of the people toward life in general and toward conventional obstetric care in particular (chapter 2).

Women with a previous VVF repair stand out as poor reproducers. As one would expect, they are liable to recurrent urinary tract infection and to disproportion but their tendency to bear low-birthweight babies, and their poor record of child survival point to a more fundamental defect. These women, predominantly uneducated Hausa-Fulani, are typically of small stature, high parity and suffer all the associated problems of severe socioeconomic deprivation. These effects can only be reversed if and when the appropriate social and health reforms are implemented.

After caesarean section, there is always the

Table 9.8. Distribution of the major maternal characteristics by previous operations

Maternal characteristic	Previous operations				
	None	Ectopic with or without caesarean section	Caesarean section	VVF repair	VVF and caesarean section
Literacy (%)	10	21	14	2	6
Emergency admissions (%)	34	4	24	22	26
Operative delivery in current pregnancy (%)	14	3	55	76	96
Low fetal birthweight in current pregnancy (%)	13	8	14	29	15
Fetal loss in current pregnancy (%)	10	3	9	16	15
Child survival from previous births (%)	75	89	73	33	31

VVF, Vesicovaginal fistula

danger of scar rupture in subsequent pregnancies. Our results show that antenatal care reduces but does not entirely eliminate the risk of uterine rupture. This could only come about if there were total acceptance of modern obstetric care. This has apparently happened among the women with formal education but not among the uneducated (chapter 2) and it helps to explain why uterine rupture, rare in the educated women, was comparatively common among the illiterates. In this series, whenever the scar ruptured, it apparently did so during labour and not before. This suggests that most uterine scars resulting from previous caesarean sections in Zaria, almost always lower segment operations, were sound. It is also possible that patients with scar rupture during pregnancy, and before the onset of labour, were not being seen in hospital because they died at home. However, close scrutiny of these Zaria results shows that even among the 10 women who had antenatal care, scar rupture could have been avoided in four of them. In one, the scar ruptured during manual removal of the placenta, in two women with disproportion, delivery by caesarean section before the onset of labour was the obvious treatment, but in fact, the operation was performed during labour in both cases Another arrived in obstructed labour in the second stage of labour.

We would have liked to know the effect a previous operation had on pregnancy spacing especially whether or not a first caesarean section or VVF repair delayed a second pregnancy Unfortunately, our data, which span only a 3½-year period, did not permit this. However, there was useful information about women who were delivered at home and reported to hospital shortly afterwards. Such women made up 9% of those with no previous operation, but under 1% of those with previous VVF repair with, or without, caesarean section The difference in these proportions could be indicative of a more fundamental difference in attitudes towards hospital care after a previous operation and it is open to various interpretations. It could be that women were rarely delivered at home after a previous operation especially VVF repair. Another possibility is that following VVF repair, subsequent deliveries at home were often uncomplicated making it unnecessary for the affected women to report to hospital afterwards. Both of these possibilities are very unlikely in the adverse conditions in which many of such women live, and in the nature of the two case reports included in this chapter. One was of a woman with previous VVF repair who defaulted once she realized that delivery by elective caesarean section was being planned The other was that of a woman with previous caesarean section for obstructed labour, who in her subsequent pregnancy avoided any obstetric care at all until it was too late to prevent a recurrence of the VVF and to save her baby. For these reasons, a more likely explanation why so few women with previous operations reported to hospital after home deliveries was that some among them, who developed major complications such as uterine rupture, most probably died at home. They were therefore not being seen in hospital, and their deaths were not recorded. There can be no complacency about the risks of subsequent pregnancies following VVF repair and caesarean sections

Meanwhile, this analysis shows that recurrent urinary tract infection carries a grave risk in pregnant women with previous VVF repair. Indeed, there was one maternal death from this cause and there may well be a case for the use of prophylactic antimicrobial agents throughout pregnancy in these cases

Lastly the excellent reproductive performance of women who had surgical treatment for ectopic pregnancy has to be explained. To do so, it is important to realize that ectopic pregnancy is often rapidly fatal unless effective treatment is given early This is a situation where, through a form of social selection, those who have ectopic pregnancy and also suffer most from the effects of gross socioeconomic deprivation and are denied access to modern health care, are simply eliminated. The survivors, by contrast, are likely to be the ones who enjoy a better standard of living and who have learnt to take good care of their health These important social advantages, which survivors from ectopic pregnancy possess, probably account for their superior reproductive performance in subsequent pregnancies.

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10. Easily identifiable congenital malformations

in collaboration with A. D. EKANEM & H. CHONG

Summary. At birth, the prevalence of easily identifiable congenital malformations was 14 per 1000 babies. Polydactyly was very common and cleft lip/cleft palate very rare as they are in other black populations. The prevalence of neural-tube defects was only 1·6 per 1000 babies and there was little to indicate that the socially disadvantaged were any more vulnerable than those with better living standards. As a group, congenital malformations contribute very little towards the poor maternal and fetal outcomes in Zaria.

Ascertainment of birth defects

Within the first 24 h after birth, every baby was systematically examined and the findings were recorded by the accoucheur. Whenever congenital malformations were found, their presence was confirmed by members of the medical staff of the department and sometimes by paediatricians. In survivors of operative deliveries, the examination was repeated before the babies were discharged home. In this particular respect, the local people themselves took a keen interest in their infants. Visitors to the maternity ward, especially grandmothers and other female relatives, were often seen examining the babies meticulously, and any blemish was promptly reported to the nursing or medical staff.

Search for upper gut atresia, by the passage of a nasogastric tube, was routine in the case of newborn babies whose mothers had hydramnios. For cultural and religious reasons autopsies were never performed

Chromosome studies were not done, hence the diagnosis of chromosome abnormalities, almost always by paediatricians, was based on clinical grounds only.

Frequency

In the survey population of 23 512 babies, 333 (1·4%) had easily identifiable congenital malformations at birth. The types of malformations, the anatomical systems involved and the number of infants affected are shown in Table 10.1. A group referred to as 'multiple systems' consisted of 19 babies (Table 10.2), of whom 17 had not less than three types of malformation. The remaining two had gross abdominal distension which made us suspect that they had multiple malformations involving several organs.

The anatomical systems most frequently affected were the musculoskeletal and the central nervous system, with polydactyly, hydrocephaly, anencephaly and spina bifida commonest.

Malformations were also classified according to whether they were minor or major Unlike major malformations (151 babies), the minor malformations (131 babies) were non-lethal and not severely handicapping. Minor malformations were polydactyly, hypospadias, epispadias, natal teeth, haemangioma, skin appendage and undescended testes. The exact nature of the defect was not stated in eight with major defects, in 21 with minor defects, and in 51 other babies (Table 10.1).

Epidemiological considerations

The aim was to obtain a rough idea of the relation between social and biological variables and certain congenital malformations. Only those malformations least likely to be missed at birth were chosen for this analysis: neural-tube defects, spina bifida, cleft lip/palate and polydactyly. Further, the choice was also restricted to babies with the one defect in polydactyly, to those with no more than two other defects in the case of neural-tube defects and to those with complete data on the social and biological variables. Table 10 3 shows that among Nigerians, the prevalance of polydactyly was unaffected by

Table 10.1. Easily identifiable malformations

Anatomical system	Malformations
Central nervous system	Anencephaly only (13)
	Anencephaly and hare lip (1)
	Spina bifida (10)
	Spina bifida and hydrocephaly (8)
	Hydrocephaly alone (25)
	Hydrocephaly with polydactyly (1)
	Hydrocephaly with talipes (1)
Eye	Bilateral corneal opacity (1)
	Cyclops (1)
Ear, face and neck	Cystic hygroma of neck (2)
	Abnormal skull with talipes (1)
Heart and circulation	Congenital cyanotic heart disease (2)
Alimentary	Cleft palate (2)
	Cleft palate and cleft lip (5)
	Intestinal obstruction (3)
	Jaw anomaly (3)
	Tracheo-oesophageal fistula (1)
Urogenital	Intersex (3)
	Hypospadias (5)
	Epispadias (1)
	Undescended testes (1)
Musculoskeletal	Achondroplasia (6)
	Achondroplasia and polydactyly (1)
	Genu recurvatum (5)
	Talipes alone (4)
	Arthrogryposis (2)
	Arthrogryposis with exomphalos (1)
	Exomphalos (3)
	Omphalocoele (1)
	Polydactyly (88)
Skin	Natal teeth (3)
	Haemangioma (2)
	Naevus (1)
	Skin appendage (1)
Chromosome	Chromosome anomalies (5)
	Chromosome anomaly with oesophageal atresia (1)
Whole fetal	Conjoined twins (3 pairs)
	Fetus papyraceous (1)
Multiple systems	Three or more anomalies in the same fetus (19)
Others	Malformations not specified but classified as minor (21), as major (8), and as neither (51)

Numbers of affected babies are shown in parentheses

Table 10.2. Multiple anomalies in 19 fetuses

Fetus no	Description of anomalies
1	Absent radius, bilateral short legs, bilateral corneal opacities
2	Intersex, imperforate anus, exomphalos, microcephaly, abnormal face, abnormal fingers and toes
3	Short curved limbs, rudimentary sex organs, abdominal distension
4	Small eyes, macroglossia, abdominal distension
5 & 6	Abdominal distension
7	Encephalocoele, harelip, polydactyly, exomphalos
8	Meningocoele, hydrocephaly, talipes, exomphalos
9	Micrognathus, talipes, two palmar creases
10	Exomphalos, hepatomegaly, bilateral enlargement of kidneys
11	Micrognathus, overlapping of fingers, trisomy 18
12	Spina bifida, talipes equinovarus, finger abnormalities including syndactyly
13	Deformity of sacrum, cloaca and external genitalia and ? bladder
14	Hydrocephaly, talipes, claw hands
15	Hydrocephaly, meningomyelocoele, bilateral talipes
16	Hydrocephaly, deformity of hips and deformity of wrists
17	Abnormal face, stunted limbs, very short umbilical cord
18	Congenital heart disease, chromosomal anomaly, polydactyly
19	Anencephaly, spina bifida, double face

place of residence, religion, ethnic group, educational or booking status. All neural-tube defects (including spina bifida) and spina bifida alone were most frequent in the unbooked and least frequent in the booked. Cleft palate/lip was very rare.

Table 10.4 relates maternal age and parity to the frequency of polydactyly, all neural-tube defects, spina bifida alone and cleft palate/lip. The prevalence of these central nervous system defects was highest in the oldest and most parous groups. No such age–parity effect was evident in polydactyly.

Pregnancy complications

Hydramnios, disproportion, prolonged labour

Table 10.3. Prevalence of certain congenital malformations by social factors

Social factor	Polydactyly	All neural-tube defects	Spina bifida alone	Cleft palate/hare lip
	Malformation (no /1000 total births)			
Residence				
Zaria	3·4 (58)	1·2 (19)	0·7 (11)	0·1 (2)
Outside Zaria	3·7 (19)	2·8 (14)	1·4 (7)	0·6 (3)
Religion				
Christian	4·2 (32)	1·2 (9)	0·5 (4)	0·0
Islam	3·0 (41)	1·7 (24)	1·0 (14)	0·4 (5)
Others	0 0	0·0	0·0	0·0
Booking status				
Booked	3·6 (26)	0·8 (11)	0 3 (4)	0·1 (2)
Unbooked	3·5 (51)	3·0 (22)	1·9 (14)	0·4 (3)
Ethnic group				
Hausa–Fulani	3·3 (35)	2·1 (23)	1·3 (14)	0·4 (4)
Other Nigerians	3·5 (39)	0·9 (10)	0·4 (4)	0·1 (1)
Others				
Formal education				
Education	5·5 (13)	1·6 (4)	0·8 (2)	0·3 (5)
None	3·3 (64)	1·5 (29)	0 8 (16)	0·0

Numbers of affected babies are shown in parentheses.

Table 10.4. Prevalence of specific congenital malformations by maternal age and parity

Maternal factor	Total no. of births	Polydactyly	All neural-tube defects	Spina bifida alone	Cleft palate/lip
		Malformation (no./1000 total births)			
Age (years)					
≤16	2464	4·5 (11)	0·4 (1)	0·0	0·4 (1)
17–19	3490	4·6 (16)	2·0 (7)	1·2 (4)	0·3 (1)
20–24	6371	2·4 (15)	1·3 (8)	0·6 (4)	0·2 (1)
25–29	5054	3·4 (17)	1·0 (5)	0·4 (2)	0·2 (1)
≥30	3760	3·5 (13)	2·9 (11)	2·1 (8)	0 0
Parity					
0	6242	4·32 (27)	1·3 (8)	0·5 (3)	0·5 (3)
1	3896	3·60 (14)	1·5 (6)	1·0 (4)	0·3 (1)
2	3410	2·93 (10)	0·3 (1)	0·0	0 0
3	2664	3·00 (8)	1·9 (5)	0·8 (2)	0·0
4	2011	2·49 (5)	0·5 (1)	0·5 (1)	0·5 (1)
≥5	3643	3·57 (13)	3·3 (12)	2·2 (8)	0·0

Numbers of affected babies are shown in parentheses.

and fetal malpresentation were the commonest pregnancy complications associated with fetal malformations. Such malformations were mostly those of the central nervous system.

Among the hydrocephalics, three had hydramnios, 14 presented with disproportion, 11 with prolonged labour, 11 with breech presentation and one with transverse lie. Among those with neural-tube defects, nine had hydramnios and seven were breech presentations.

Mode of delivery

Table 10.5 shows the mode of delivery in babies with major and minor defects and in those without any visible malformations. The distribution of those without malformations and those with minor malformations were similar and they differed from the pattern for those with major malformations, among whom breech delivery, embryotomies and the other deliveries were all very noticeable However, overall, congenital malformations played only a small part in the abnormal deliveries in the survey population. All embryotomies in the major malformations were craniotomies on hydrocephalics. Of the five other deliveries, all were laparotomies and deliveries in the presence of rupture of the uterus, associated with neglected obstructed labour due to hydrocephaly in four patients and conjoined twins in one.

In those born by caesarean section, the presence of fetal malformations was unsuspected before delivery. The malformations were spina bifida (2), hydrocephaly (6), multiple systems (4), tracheo-oesphageal fistula (1), intersex (1), arthrogryposis (1), achondroplasia (1), exomphalos (1) and polydactyly (7)

Breech deliveries were principally associated with central nervous system defects and limb defects.

Fetal outcome and fetal birthweight

Low birthweight and fetal loss were more prevalent in babies with malformations than in those without (Table 10.6)

The perinatal mortality rates per 1000 were 100 in those without malformations, 69 in the presence of minor malformations, 748 in major malformations and 372 in babies where the malformations present were not stated

Table 10.7 shows fetal outcome in the presence of the most frequent malformations. In this context, live births meant survivors who were still alive on discharge from the hospital. None of the babies with anencephaly and exomphalos survived. In addition to those shown in Table 10.7, there were at least 12 other babies with major handicaps who were discharged from hospital between 1 and 30 days after birth. They include babies with the following malformations—bilateral absent radius with corneal opacities, cleft lip and cleft palate, cyanotic heart disease, jaw anomalies, arthrogryposis and various forms of talipes. During their period in hospital, three had already recovered from bacterial infections, one from neonatal jaundice and another from fracture of the humerus. Because further follow-up was not possible, the ultimate fate of these survivors among the malformed babies was not known.

Among those with achondroplasia, the only survivor was the heaviest at birth with birthweight of 4·15 kg, born by caesarean section for brow presentation. In the rest, death was associated with hydramnios in three, with APH in one, and with low birthweight in five (1·75–2·50 kg).

Comment

This report, based on congenital malformations seen in the hospital, is incomplete for obvious reasons too well known to discuss here. All the same the report does give a rough indication of the types of malformations seen at birth, and it also confirms much that is already known about fetal malformations in Negro populations. For

Table 10.5. Mode of delivery and congenital malformations

	Malformation (singletons only)			Malformation (multiple births)		
Mode of delivery	None	Minor	Major	None	Minor	Major
Spontaneous	18 514 (85·4)	98 (83·1)	79 (61·2)	1022 (68·1)	11 (84·6)	11 (50·0)
Vaginal breech	368 (1·7)	4 (3·4)	19 (14·7)	343 (22·9)	2 (15·4)	7 (31·8)
Forceps	498 (2·3)	3 (2·5)	5 (3·9)	31 (2·1)	0	1 (4·5)
Caesarean section	1948 (9·0)	11 (9·3)	13 (10·1)	85 (5·7)	0	0
Destructive operations	212 (1·0)	2 (1·7)	8 (6·2)	8 (0·5)	0	1 (4·5)
Other	150 (0·7)	0	5 (3·9)	11 (0·7)	0	2 (9·1)
Total number	21 690	118	129	1500	13	22

Results are numbers, with percentages in parentheses.

Table 10.6. Fetal birthweight and outcome by congenital malformations (singleton and multiple births combined)

	Type of malformation							
	None		Minor		Major		Not stated	
Birthweight (kg)	Live	Deaths	Live	Deaths	Live	Deaths	Live	Deaths
≤2·00	554	849	5	3	5	38	5	9
2·01–2·50	1971	326	19	3	5	18	8	4
2·51–3·00	6057	468	37	2	11	23	6	1
3·01–3·50	7902	393	38	1	9	17	4	1
≥3·51	3573	193	22	0	7	14	4	1
Total no. of babies weighed	20 057	2229	121	9	37	110	27	16
% with low birthweight	12·6	52·7	19·8	66·7	27 0	50·9	48·1	81·3

Results are numbers of babies

Table 10.7. Specific congenital malformations and fetal outcome

	Number of babies			
Type of malformation	Total	Live*	Stillbirths	Neonatal deaths
Anencephaly	15	0	13	2
Spina bifida	20	3	10	7
Hydrocephaly	31	2	22	7
Intersex	5	4	0	1
Genu recurvatum and talipes	18	10	7	1
Achondroplasia	7	1	5	1
Exomphalos	6	0	1	5
Chromosome anomaly	8	4	1	3
Polydactyly	88	86	1	1
All malformed babies	333†	192	83	57

*Alive on discharge from hospital
†Fetal outcome was unknown in one baby

example, polydactyly was common whereas cleft palate/lip was rare (Leck 1983).

In polydactyly, the extra digits varied in size from full-sized digits to small excrescences but the majority were pedunculated appendages about 0·5–1·0 cm long, and always attached close to the base of the little finger or fifth toe. All but the full-sized extra digits were tied firmly at the base within the first 24 h after birth. Those treated in this way came off within days, a scab formed and healing was complete within 2 weeks.

Neural-tube defects are thought to be associated with social deprivation but in this survey, the uneducated do not appear to be particularly vulnerable compared with those with formal education. The fact that neural-tube defects were more common in the Hausa-Fulanis presumably reflects not differences in prevalence as such, but the fact that obstetric complications associated with the presence of the fetal defects, such as fetal malpresentation leading to obstructed labour, brought the mothers into hospital. The same may also be true in the case of the older unbooked mothers.

A few women were noted to have certain birth defects themselves, particularly syndactyly, polydactyly, achondroplasia, talipes and cleft lip. In their case the defects had obviously remained uncorrected. Unfortunately, defects in the mothers were not coded in our records and so it is impossible to say what the frequencies of any such malformations were in the adult population.

Lastly, the most important point here is that though congenital malformations did obstruct labour and thereby threaten maternal health, these malformations contribute very little to the poor maternal and fetal outcomes in this survey. In working towards improving perinatal results, teratology is not yet an area of priority.

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11. Perinatal mortality

in collaboration with U. G. LISTER, C. E. ROSSITER & H. CHONG

Summary. The perinatal mortality rate in all singleton births was 103 per 1000; 67% of all perinatal deaths were stillbirths and in 77% of stillbirths, intrauterine death had already occurred before admission to hospital. Nine per cent of live births but 40% of stillbirths and 50% of neonatal deaths were of low birthweight (≤2·5 kg). The principal obstetric causes of perinatal deaths were obstructed labour and its consequences, anaemia, antepartum haemorrhage, eclampsia and low fetal birthweight. Nearly half of all perinatal deaths were associated with complicated deliveries of which vaginal breech delivery was by far the most hazardous. Both the proportion of babies with low birthweight and the perinatal mortality rates rose dramatically and progressively with haematocrit <0·30. A raised perinatal mortality rate was also associated with raised haematocrit >0·40. Of the biosocial factors influencing perinatal health, lack of antenatal care, residence outside Zaria, early teenage pregnancy and high parity exerted the most deleterious effect and literacy and antenatal care the most favourable effect on pregnancy outcome.

It is not the purpose of this analysis to go into detailed discussion of the pathological causes of perinatal death. Rather, the aim here is to focus attention on the clinical, cultural and social factors influencing fetal survival and to interpret the statistics on birthweight in singleton births.

Birthweight, place of birth and fetal outcome

Birthweights for singleton babies ranged between 0·6 and 4·45 kg (Table 11.1). As expected, live babies (excluding neonatal deaths) tended to weigh more than the others and a much smaller proportion weighed ≤2·5 kg (9·3% compared with 43·5%). A significantly greater proportion of the neonatal deaths than of the stillbirths weighed ≤2·5 kg ($\chi^2 = 14$, d.f. = 1, $P<0{\cdot}0001$). Table 11.2 shows that babies born in hospital had a better survival rate than babies born outside hospital. Most of the women who reported to hospital after giving birth at home did so because they or their newborn babies were ill. Stillbirths exceeded neonatal deaths by just over 2 to 1 irrespective of place of birth. The mean birthweights in the various groups were: 3·08 kg (all singleton births); 2·84 kg (5646 unbooked Hausa–Fulanis); 3·07 kg (4278 booked Hausa–Fulanis); 3·00 kg (829 unbooked other Nigerians) and 3·23 kg (10 093 booked other Nigerians).

Birthweight, fetal sex and fetal outcome

Of the singleton births in hospital, 10 444 were male, 9530 female and in 90 babies sex was not recorded; 35 males and 26 females were not weighed at birth. The proportions of live births, intrauterine deaths on admission, intrauterine deaths after admission and neonatal deaths were 89·8%, 5·2%, 1·5% and 3·5% in the male births compared with 91·6%, 4·4%, 1·4% and 2·6% in the females. In the birthweight groups ≤2·50 kg, 2·51–3·00 kg, 3·01–3·50 kg, 3·51–4·00 kg, and >4·00 kg, the proportion of babies were 11·1%, 25·4%, 41·3%, 19·1% and 3·1% for males compared with 13·9%, 33·7%, 38·2%, 12·5% and 1·7% for females. The proportion of babies weighing ≤2·5 kg was 7·7% for males and 10·9% for females among live births, and 40·6% for males and 46·5% for females among perinatal

Table 11.1. Fetal outcome by birthweight (singleton births in hospital)

Birthweight (kg)	Live birth	IUD on admission	IUD after admission	Early neonatal death	Late neonatal death
≤1·00	7 (0·0)	34 (3·5)	16 (5·6)	25 (4·4)	1 (2·2)
1·01–2·00	275 (1·5)	194 (20·2)	56 (19·4)	179 (31·7)	19 (41·3)
2·01–2·50	1403 (7·7)	157 (16·3)	49 (17·0)	72 (12·8)	7 (15·2)
2·51–3·00	5408 (29·9)	250 (26·0)	63 (21·9)	127 (22·5)	12 (26·1)
3·01–3·25	3674 (20·3)	98 (10·2)	37 (12·8)	56 (9·9)	2 (4·3)
3·26–3·50	3870 (21·4)	112 (11·6)	29 (10·1)	61 (10·8)	2 (4·3)
3·51–4·00	3025 (16·7)	95 (9·9)	25 (8·7)	41 (7·3)	3 (6·5)
≥4·01	453 (2·5)	22 (2·3)	13 (4·5)	3 (0·5)	0
Not recorded	45	28	13	7	0
Total number weighed	18 115	962	288	564	46
Median birthweight (kg)	3·14	2·70	2·69	2·54	2·27

Results are numbers, with percentages in parentheses.
IUD, Intrauterine death.

Table 11.2. Fetal outcome by place of birth (singleton births only)

Fetal outcome	Number	% of group	% of total
Hospital births			
Live birth	18 159	90·5	82·7
IUD on admission	990	4·9	4·5
IUD after admission	301	1·5	1·4
Neonatal death in first week	571	2·9	2·6
Neonatal death later	46	0·2	0·2
Home births*			
Live birth	1525	80·8	6·9
Stillbirth	251	13·3	1·2
Neonatal death	111	5·9	0·5

* Born before arrival at hospital (place of birth unknown for four babies).
IUD, Intrauterine death

deaths. Perinatal deaths per 1000 deliveries were 371 for males and 277 for females in the low birthweight (≤2·50 kg) babies, and 67 for males and 51 for females in normal birthweight babies.

Maternal age, birth order and fetal outcome

Perinatal mortality rate was lowest (<90 per 1000) in the women aged between 20 and 29 years at parities of 1–4 and it was highest at parities ≥5 (150 per 1000) and in early teenage primigravidae aged ≤15 years (171 per 1000). The details are presented in Chapter 4.

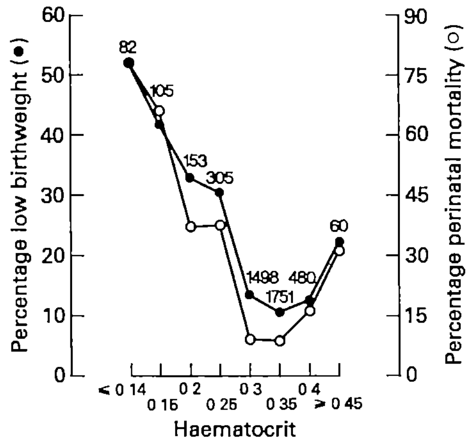

Fig. 11.1. Maternal haematocrit at delivery, low fetal birthweight and perinatal mortality in singleton births.

Maternal haematocrit levels and fetal outcome

Many obstetric complications affect fetal mortality through their effect on fetal birthweight. Fig. 11.1 shows this relation for those 4434 singleton babies whose mothers had their haematocrit levels (range 0·05–0·60) determined within 2 weeks of delivery. Women with antepartum haemorrhage were excluded from this analysis. Both the proportion with birthweight ≤2·50 kg and the perinatal mortality rates rose dramatically and progressively with haematocrit <0·30; a somewhat raised perinatal mortality rate was also associated with raised haematocrit >0·40.

Table 11.3. Effect of prolonged labour and disproportion on fetal outcome (singleton births in hospital)

Duration of labour	Fetal outcome	No disproportion			Disproportion		
		Number	% of group	% of total	Number	% of group	% of total
Not prolonged (<24 h)	Live birth	16 659	92·5	90·4	739	82·7	45·4
	IUD on admission	668	3·7	3·6	68	7·6	4·2
	IUD after admission	244	1·4	1·3	13	1·5	0·8
	Neonatal death	434	2·4	2·3	73	8·2	4·5
Prolonged (≥24 h)	Live birth	297	68·9	1·6	461	62·8	28·3
	IUD on admission	77	17·9	0·4	177	24·1	10·9
	IUD after admission	19	4·4	0·1	25	3·4	1·5
	Neonatal death	38	8·8	0·2	71	9·7	4·4

IUD, Intrauterine death

Table 11.4. Maternal anaemia and fetal outcome (singleton births)

Haematocrit level	Total births	Live births	IUD on admission	IUD after admission	Neonatal deaths
≤0·14	75	24 (32·0)	33 (44·0)	3 (4·0)	15 (20·0)
0·15–0·18	93	29 (31·2)	44 (47·3)	7 (7·5)	13 (14·0)
0·19–0·25	337	222 (65·9)	74 (22·0)	18 (5·3)	23 (6·8)
0·26–0·29	750	664 (88·5)	40 (5·3)	22 (2·9)	24 (3·2)
≥0·30	18 770	17 201 (91·6)	784 (4·2)	245 (1·3)	540 (2·9)

Results are numbers, with percentages in parentheses.
IUD, Intrauterine death.

Obstetric complications and fetal outcome

There were 2650 major obstetric complications (Appendix 11.1) reported among all 1908 perinatal deaths (Table 11.1) in this series; this meant that in many instances, at least two obstetric complications were present in a single perinatal death.

Disproportion was the commonest obstetric complication and was also the leading cause of perinatal death. Table 11.3 shows that labour was prolonged in nearly half of the women with disproportion. Where prolonged labour and disproportion were found together, the combination worsened fetal prognosis.

Apart from disproportion and prolonged labour, the other common causes of perinatal deaths were anaemia, antepartum haemorrhage (APH), fetal malpresentation, uterine rupture, eclampsia, low fetal birthweight and complicated deliveries. As many as 90% of all babies whose mothers developed obstetric fistula died, and fetal loss was over 35% for nearly half of the obstetric complications listed in Appendix 11.1.

Table 11.4 shows the influence of maternal anaemia on fetal outcome. The haematocrit values were those obtained not necessarily at delivery, but at the woman's first attendance at the hospital either to book for antenatal care or to seek emergency treatment. As maternal haematocrit fell, the proportion of both stillbirths and neonatal deaths rose. Fig. 11.1 shows similar information for haematocrit at delivery.

Low fetal birthweight and obstetric complications

It can be deduced from Appendix 11.1 that women with anaemia, associated medical diseases or breech presentation had a frequency of low fetal birthweight that was nearly twice that in all the singleton births. Furthermore, in association with eclampsia, major congenital malformations or APH, the frequency of these small infants was even higher.

Table 11.5. Prevalence of disproportion by mode of delivery and low fetal birthweight (≤2·5 kg) (singleton births in hospital)

	Prevalence of disproportion (%)			
	Live births		Perinatal deaths	
Mode of delivery	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg
Spontaneous delivery	0·5 (1439)	0·4 (14 370)	0·6 (542)	6·7 (421)
Vaginal breech	0 (34)	0 (185)	1·2 (83)	1·2 (81)
Forceps	0 (54)	7·3 (354)	5·6 (36)	25·4 (59)
Caesarean section	37·3 (158)	68·4 (1503)	22·2 (81)	57·3 (211)
Embryotomy	—	—	73·8 (42)	77·1 (175)
Other deliveries	—	83·3 (18)	4·0 (25)	51·9 (104)

Numbers of deliveries are shown in parentheses.

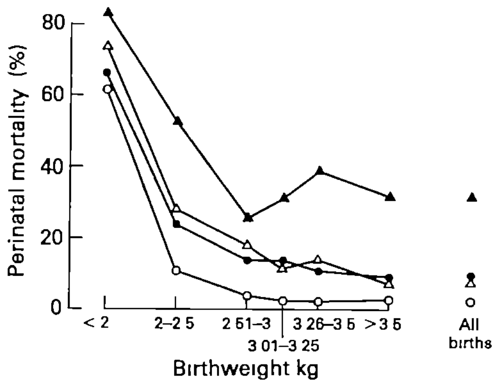

Fig. 11.2. Mode of delivery (○ spontaneous; ▲ breech, △ forceps; ● caesarean section), fetal birthweight and perinatal mortality rate among singleton births.

Complicated deliveries and fetal outcome

There were four women with advanced extra-uterine pregnancy and all four babies were stillborn. Thirteen percent of live births but 48% of all perinatal deaths were associated with complicated deliveries, a situation which was inevitably worsened by the fact that 10% of the women arrived in the second stage of labour and 4% in the third stage. Indeed, in 15% of all 3203 women who had operative deliveries, the operations were performed when intrauterine fetal death had already occurred before arrival at the hospital Disproportion was the principal underlying obstetric factor in difficult vaginal delivery and in abdominal delivery, especially where the babies were of normal birthweight (Table 11.5).

Fig. 11.2 shows that vaginal breech delivery carried the highest mortality rate. After exclusion of all babies who were already dead on admission, the corrected death rates for low-birthweight and normal-birthweight babies were 16·6% and 1·4% respectively for spontaneous delivery, 28% and 10% for caesarean section, 31% and 10% for forceps delivery and 54% and 17% for vaginal breech delivery.

Fetal outcome among healthy women

Of all 14 225 booked women with singleton births, 3308 (23%) had one or more of the following complications. anaemia, threatened abortion, pre-eclampsia, hypertension, eclampsia, haemoglobinopathy, APH, associated diseases The rest are here considered healthy, although 274 had disproportion.

The operative delivery rate was only 5·5% in the healthy women compared with 25·1% in the booked women with antenatal complications (the rates in the two groups were 1·6 and 1·8% for vaginal breech delivery, 1·1 and 3·7% for forceps, 2·6 and 19·0% for caesarean section, 0·1 and 0·3% for destructive operations, 0·1 and 0·3% for other deliveries).

In the healthy women, live births, intrauterine deaths before admission, intrauterine deaths after admission and neonatal deaths were 97·8%, 0·7%, 0·5% and 1·0% respectively of total births compared with 92·6%, 2·7%, 1·6% and 3·1% respectively in women with antenatal complications. The proportions of low-birthweight babies born in hospital to healthy women were 5·9% of the live births and 36·6% of the

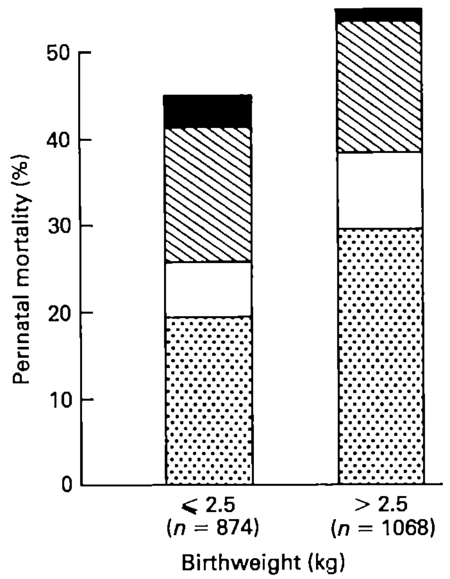

Fig. 11.3. Fetal birthweight, place and time of perinatal death in singleton births ■ Born before arrival; ▨ neonatal deaths; □ stillbirth, intrauterine death after admission; ⬚ stillbirth, intrauterine death before admission

perinatal deaths compared with 9·4% and 53·4% of the babies born to women with antenatal complications.

Biosocial factors and fetal outcome

Only those women and babies with complete data on every biosocial variable are included in Appendices 11.2–11.7. This explains the minor discrepancies between certain numbers in these and earlier tables. Appendix 11.2 relates fetal outcome and birthweight to biosocial factors. Normal-birthweight fetuses who were dead *in utero* before admission constituted the largest (31%) of the eight groups of perinatal deaths (Fig. 11.3). These occurred mainly in uneducated Hausa–Fulanis who have had no antenatal care, and nearly two-thirds were from outside Zaria itself.

In Appendix 11.3 major antenatal complications are considered. Substantial proportions of women with these antenatal complications were booked. Indeed, 27% of all eclamptics were booked, although the disease was rare in those with formal education. However, fetal deaths associated with nearly all of those complications occurred largely among the unbooked uneducated Hausa–Fulanis. Fetal loss associated with anaemia was particularly pronounced in those living outside Zaria

Appendix 11.4 concerns complications during labour. Perinatal deaths due to disproportion and its consequences were again almost entirely confined to the uneducated and unbooked Hausa–Fulanis from outside Zaria. No educated woman developed obstetric fistula, and none of the few non-Nigerian women developed such a fistula.

Appendices 11.5 and 11.6 consider modes of delivery. The results of breech delivery were uniformly poor. Of the babies born by caesarean section, those that survived were equally distributed among the booked and unbooked groups, but the fetal deaths were again confined largely to the uneducated Hausa–Fulanis who had had no antenatal care.

Appendix 11.7 shows a very wide variation between the sociocultural groups for fetal outcome particularly in the perinatal mortality rates. The differences are striking with the unbooked, Hausa–Fulani, uneducated, those of Islamic faith and those resident outside Zaria all having high perinatal death rates. Among Zaria residents, perinatal mortality rate was highest in those from the Old City.

Discussion

Several points made here about the social epidemiology of child-bearing are not new (Baird 1949; Chamberlain 1979; Alberman 1980). However, it is the scale of the loss of fetal life which is deeply disturbing. Many factors, some very fundamental in nature, are involved and they will now be examined in relation to each of the common obstetric complications. First, it is pertinent to point out that with few exceptions all the principal obstetric complications were found in women of all sociocultural groups but the proportion of those affected and the proportion of those who lost their babies varied very widely In relation to practically every obstetric complication, those who had booked for antenatal care fared better than those who failed to do so; the same was also true of the other Nigerians compared with the Hausa–Fulanis. Furthermore, in an area where communications systems are inadequate, it was clearly advantageous to be resident in Zaria rather than outside Zaria, but it was formal education which carried the best prospects for perinatal health.

Disproportion is the major obstetric problem in Northern Nigeria and, as this report has shown, those who bore the brunt of the effects of disproportion were the uneducated Hausa–Fulani who were admitted as an emergency. Elsewhere (chapter 4) it has also been shown that women from that sociocultural background comprise the vast majority of the shortest women and hence also of those with pelvic contraction.

Several traditional customs heighten the problems of disproportion in the Zaria area. The point at which each of these customs operates in relation to disproportion will now be discussed. Because many girls start childbearing when they are not fully grown, and because of stunting in growth caused by poor nutrition and frequent childhood infections, pelvic contraction is common. Women of child-bearing age, including pregnant women, are often semi-secluded and they are therefore denied the benefits of antenatal care which is freely available to all Zaria residents. As a result, disproportion and fetal malpresentations remain undetected during the antenatal period. In the case of early teenage primigravidae, growth in height and pelvic size does not take place as it would have done in some, had they been booked for antenatal care and therefore taken malarial chemoprophylaxis and iron and folic acid supplements (chapter 6).

Other traditional customs are harmful by their effect in delaying the diagnosis and treatment of disproportion. The first of these customs is a strongly held belief that home delivery is best for all primigravidae, especially the youngest, but labour at their home lacks expert supervision (Trevitt 1973). Consequently, during labour, the very women who are at the greatest risk of disproportion are left without expert care and so signs of impending obstruction remain unrecognized. In matters affecting a wife, custom decrees that decision-making be the preserve of her husband. This custom has serious implications during difficult labour. In such a situation, it is the husband who decides when his wife is to be transferred to hospital If the husband happens to be away from home, those around are often unwilling to take on the responsibility of arranging for the transfer of his wife to hospital. Further action must await the husband's return. Delays from this cause have been known to last for 3 days or longer even among Zaria residents.

Nigerians, especially those with no formal education, avoid operative deliveries as much as they can. Even when labour gets obstructed, permission for operative delivery is sometimes very difficult to secure. Under these circumstances, obstruction is nearly always advanced when it is eventually relieved by operation. Inevitably, such operations become difficult to perform and they are often carried out when fetal life is already in serious jeopardy, adding to the increase in fetal loss during complicated deliveries.

Some of the factors working against maternal and fetal interest in disproportion also apply to other obstetric complications needing operative delivery such as APH and fetal malpresentations, but there were additional elements. For example, in APH from other causes, the haemorrhage was as a result of a gishiri cut (chapter 2) in nearly 30% of cases.

Turning to anaemia, it is understandable why this disease was very common in the emergency admissions (Appendix 11.3): they had not received protection against malaria and against both iron and folic acid deficiency (Fleming *et al.* 1984). Among the booked and the educated women, anaemia occurred largely because booking was too late for prophylaxis to be effective, although six women had haemoglobin SC disease and 22 had sickle cell anaemia (HbSS). Malaria, which is the principal cause of anaemia in pregnancy in Zaria, is holoendemic. In pregnant Nigerian women anaemia from malaria commonly develops between 16 and 24 weeks of gestation (Gilles *et al.* 1969). But booking for antenatal care is often delayed until after the 20th week and this explains why some women are already anaemic when they first report for antenatal care. Fetal loss among the anaemic is a result of intrauterine growth retardation (Harrison & Ibeziako 1973), intrauterine fetal death and prematurity (Llewellyn-Jones 1965).

Of equal interest to consideration of maternal anaemia is the relation between maternal haematocrit levels, low birthweight and perinatal mortality shown in Fig. 11.1 The dramatic and progressive rise in perinatal mortality rates and in the proportions of low-birthweight babies with haematocrit <0·30 is very striking. The finding should help bring to an end the controversy over the level of haematocrit below which anaemia in pregnancy should be diagnosed (Baker & de Maeyer 1979) It is therefore suggested that the haematocrit of 0·30 should be accepted as the lowest limit of normal. Fig 11 1 also shows that above the haematocrit of 0·40 fetal outcome gets worse again and this is partly because of the association of haemoconcentration with eclampsia, severe pre-eclampsia and dehydration.

Eclampsia in Zaria is often linked with disproportion and hence with the uneducated Hausa–Fulani (Appendix 11.3). Furthermore, the onset of eclampsia is often rapid and the progression from pre-eclampsia to eclampsia could take place in a matter of minutes. This explains why as many as 27% of all the eclamptics (Appendix 11.3) were booked and why early teenage primigravidae, prone as they are to disproportion and prolonged labour, are particularly vulnerable to eclampsia. Measures aimed at averting prolonged labour will also reduce fetal loss from eclampsia.

Low birthweight contributes greatly to perinatal death as it does everywhere else. However, in interpreting these data on low birthweight, it was impossible to tell how much of it was due to fetal growth retardation and how much to prematurity. Illiterate Nigerian women do not keep reliable menstrual records and routine clinical assessment of gestational age at birth was not carried out as was done by Brueton (1975) for his study of 850 babies in Zaria.

Fetal outcome in the presence of pre-eclampsia was better than it was for all other major obstetric complications (Appendix 11.3) largely because of the beneficial effect of antenatal care. There were far more women with pre-eclampsia among the booked than among the unbooked admissions, whereas in conditions such as eclampsia and disproportion, the position was the reverse (Appendices 11.3 and 11 4).

It is fair to say that the prevailing conditions in Zaria (chapter 2) meant that this analysis of obstetric causes of fetal deaths in Zaria underestimates the full extent of perinatal deaths from major fetal malformation. Even so, the contribution fetal malformations made to the overall fetal loss is very small, and most of the obvious lethal malformations were defects of the central nervous system (chapter.10)

The much improved fetal outcome in the group of healthy women calls for comment. It is indicative of what can happen if basic antenatal care is applied widely even without resort to high-technology medicine. In terms of their much higher perinatal mortality rates, a sharp difference exists between those women classified as Hausa–Fulani, uneducated, unbooked, resident outside Zaria or of Islamic faith and the rest of the population surveyed. This reflects differences in life style and also, to a lesser extent, problems brought about by poor communication systems.

Conclusion

This analysis has highlighted certain facts about the present state of perinatal health in the Zaria area. Anaemia, and conditions requiring operative delivery especially disproportion, haemorrhage and eclampsia, were very common Among the perinatal deaths, three-fifths were of normal birthweight and half were dead *in utero* even before the affected woman reached the hospital. Of those who needed operative delivery, 45% were from outside Zaria.

Furthermore, operative delivery rates (>50% abdominal) were about 30% for the unbooked and 25% for the booked women with antenatal complications, compared with only about 5% for the booked women who were healthy during pregnancy. Likewise, the perinatal death rate per 1000 deliveries was 243 for the unbooked, 74 for booked women with antenatal complications compared with only 22 for booked women who were healthy during pregnancy.

It seems obvious that to reduce fetal loss in this environment, emphasis must shift towards achieving a situation where an increasing proportion of women are healthy during pregnancy and where operative deliveries can be performed when conditions for doing so are optimal for both mother and baby. So, if perinatal health is to improve, there are two short-term needs: one is to develop antenatal care services and persuade people to use them; the other is to develop facilities for operative deliveries, especially caesarean section, in other hospitals outside Zaria. Such peripheral hospitals and health centres exist outside Zaria but all are very seriously hampered by an acute shortage of adequately trained personnel, especially nurses and midwives. A major reason for this shortage is that only about 1% of the indigenous female population receives formal education (chapter 3).

In the final analysis, therefore, to improve perinatal health, the eradication of mass illiteracy through formal education is absolutely vital. Social development of the kind which will reduce perinatal mortality to reasonable levels is simply not possible in the face of mass illiteracy and large-scale social and maternal deprivation (Lancet 1983).

Appendix 11.1. Prevalence of obstetric complications by fetal outcome and low birthweight (≤2·5 kg) (singleton births in hospital)

	Live birth		IUD on admission		IUD after admission		Neonatal death		Fetal death rate
Obstetric complication	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg	
Number of babies	1685	16 430	385	577	121	167	303	307	
Anaemia	8·4	4·9	27·3	17·3	19·8	16·8	15·5	9·8	25·4
Associated diseases									
Infective	2·4	1·6	3·9	1·9	4·1	1·8	6·6	2·6	17·0
Non-infective	2·2	1·0	2·1	1·9	1·7	0·0	3·6	0·3	14·1
Pre-eclampsia	7·8	6·0	6·8	6·2	14·0	11·4	6·3	11·1	11·8
Hypertension	0·7	0·7	1·3	0·7	1·7	1·2	1·7	0·3	13·0
Eclampsia	5·2	1·2	6·2	7·1	11·6	3·6	8·6	15·0	36·5
Antepartum haemorrhage									
Placenta praevia	2·0	0·5	7·5	6·1	9·9	9·6	8·6	3·6	53·6
Placental abruption	0·6	0·2	16·4	9·2	10·7	9·0	1·3	2·0	80·8
Other causes	2·5	0·8	10·9	4·2	9·9	6·0	5·9	2·6	38·6
Disproportion	3·9	6·9	8·3	35·0	7·4	15·6	4·0	41·4	26·0
Prolonged labour	4·9	4·1	12·7	33·3	20·7	9·6	4·6	30·6	34·4
Malpresentation									
Breech	2·4	1·4	12·2	10·4	12·4	16·8	8·6	6·8	40·4
Occipitoposterior	2·2	2·4	1·0	2·6	2·5	3·0	3·6	10·1	13·8
Face or brow	0·1	0·3	1·3	1·4	0·8	0·6	0·3	1·0	29·2
Transverse	0·3	0·2	4·2	7·5	0·8	1·8	1·3	1·0	62·0
Uterine rupture	0·0	0·2	4·7	16·6	0·0	5·4	2·0	1·6	79·6
Cord prolapse	0·2	0·2	2·9	6·2	2·5	9·6	0·7	1·0	67·0
Maternal VVF	0·1	0·0	1·3	6·4	0·8	1·8	0·0	2·3	94·0
Congenital defects·									
Minor	0·8	0·6	0·5	0·2	0·0	0·6	0·3	0·3	3·8
Major	0·3	0·1	4·4	2·9	8·3	7·2	5·0	6·2	77·3

Results are percentages
IUD, Intrauterine death, VVF, Vesicovaginal fistula

Appendix 11.2. Biosocial factors by fetal outcome and low birthweight (≤2·5 kg) (singleton births in hospital)

	Live births		IUD on admission		IUD after admission		Neonatal deaths	
Biosocial factors	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg	≤2·5 kg	>2·5 kg
Number of babies	1685	16 430	385	577	121	167	303	307
Booking status:								
Booked	54·3	77·9	21·3	15·1	30·6	39·5	34·7	33·6
Unbooked	45·6	21·9	78·7	84·9	69·4	60·5	65·3	65·5
Ethnic group								
Hausa–Fulani	63·3	39·3	84·4	88·9	82·6	70·7	72·9	79·8
Other Nigerians	36·0	59·6	15·1	11·1	17·4	28·7	25·4	18·9
Education								
Formal	6·1	13·3	1·8	1·9	8·3	7·8	5·0	3·6
None	93·3	85·8	96·9	97·4	91·7	91·6	94·4	96·1
Religion								
Christian	24·6	41·1	8·8	5·9	13·2	20·4	18·2	13·7
Islam	71·8	54·6	89·4	92·5	86·0	86·8	77·9	85·3
Residence								
Zaria								
Old City	12·6	10·3	6·0	10·7	12·4	9·0	11·6	5·5
Sabongari	18·6	31·1	14·3	6·9	16·5	16·2	15·8	15·6
Tundun Wada	13·1	16·8	6·0	3·3	6·6	9·6	12·2	10·7
Samaru	11·5	17·4	5·5	4·3	9·1	8·4	11·6	5·9
Other areas	10·6	9·2	6·5	6·4	12·4	10·2	8·6	6·8
Outside Zaria	30·4	15·3	61·8	68·3	43·0	46·7	40·3	53·4

Results are percentages

Appendix 11.3. Biosocial factors by major antenatal complications (singleton births in hospital)

	Anaemia		Pre-eclampsia		Eclampsia		Antepartum haemorrhage		Fetal malpresentation	
Biosocial factor	Live	Dead	Live	Dead	Live	Dead	Live	Dead	Live	Dead
Total numbers	934	318	1097	147	271	156	311	378	770	335
Booking status										
Booked	76·1	13·2	70·0	36·1	33·2	18·6	47·6	17·5	59·6	26·6
Unbooked	23·9	86·8	30·0	63·9	66·8	81·4	52·4	82·5	40·4	73·4
Ethnic group										
Hausa–Fulani	43·5	93·7	53·5	76·9	83·8	94·9	65·6	88·6	58·0	83·3
Other Nigerians	56·0	6·3	45·6	23·1	15·9	5·1	33·1	11·1	41·3	16·4
Non-Nigerians	0·3	0·0	0·7	0·0	0·4	0·0	1·0	0·3	0·4	0·3
Not stated	0·2	0·0	0·2	0·0	0·0	0·0	0·3	0·0	0·3	0·0
Education										
Formal	13·9	0·9	17·8	7·5	2·2	1·3	13·5	1·6	10·5	3·3
None	86·1	99·1	82·2	92·5	97·8	98·7	86·5	98·4	89·5	96·7
Religion										
Christian	39·6	5·3	33·5	17·0	10·3	2·6	23·5	7·7	29·7	9·6
Islam	57·0	94·0	63·8	82·3	86·7	96·8	73·0	91·3	67·0	89·3
Others	3·4	0·6	2·6	0·7	3·0	0·6	3·5	1·0	3·2	1·1
Residence										
Zaria										
Old City	9·5	6·9	11·7	10·9	22·5	13·5	10·9	10·1	11·7	10·4
Sabongari	32·4	8·2	25·3	15·0	13·7	7·7	18·0	9·0	22·3	12·8
Tundun Wada	15·5	4·4	18·6	10·9	13·3	7·1	11·6	6·3	13·8	6·3
Samaru	13·1	2·8	15·1	10·9	5·9	2·6	14·8	6·9	11·3	5·4
Others	9·7	6·0	9·2	10·9	10·0	10·9	11·6	5·0	9·2	7·5
Outside Zaria	19·7	71·7	20·1	41·5	34·7	58·3	33·1	62·7	31·7	57·6

Results are percentages.

Appendix 11.4. Biosocial factors by complications of labour (singleton births in hospital)

	Disproportion		Prolonged labour		Uterine rupture		Cord prolapse		Obstetric fistula	
Biosocial factors	Live	Dead	Live	Dead	Live	Dead	Live	Dead	Live	Dead
Total numbers	1163	409	725	380	34	133	33	67	3	56
Booking status										
Booked	45·1	10 3	29 7	7·9	38·2	8·3	57·6	29 9	0·0	5·4
Unbooked	54·9	89·7	70 3	92 1	61 8	91·7	42·4	70·1	100·0	94·6
Ethnic groups										
Hausa–Fulani	71·6	91·4	77·5	93·7	85·3	92·5	54·5	80·6	100·0	92·9
Other Nigerians	28·1	8·6	22·2	6·3	14 7	7·5	45 5	19·4	0·0	7·1
Non-Nigerians	0·2	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Not stated	0·1	0·0	0·1	0·0	0·0	0·0	0·0	0·0	0·0	0 0
Education										
Formal	6·3	1·7	5 4	1 1	2·9	1·5	0·0	1·5	0 0	0·0
None	93·7	98·3	94·6	98·9	97·1	98·5	100·0	98·5	100·0	100·0
Religion										
Christian	19·5	6·4	15 4	3 4	8·8	3·0	36·4	13·4	0·0	1 8
Islam	78·3	92·9	83·0	95 3	88 2	96 2	63·6	82·1	100·0	96·4
Others	2·1	0·7	1·5	1·3	2·9	0·8	0·0	4 5	0·0	1·8
Residence										
Zaria										
Old City	11·6	9·8	12·0	7·6	11 8	5 3	3·0	11·9	0·0	1·8
Sabongari	17·5	5·1	11·6	4·7	14·7	3·8	33·3	11·9	33·3	0·0
Tundun Wada	10·1	2·4	7·9	3 2	5 9	3·8	12·1	6·0	0·0	0·0
Samaru	9·2	3·2	7·2	2·1	2·9	1·5	18·2	10·4	0·0	1 8
Others	8·5	5·6	8·3	5·5	2·9	7·5	6·1	4 5	33 3	0·0
Outside Zaria	43·2	73·8	53·1	76 8	61 8	78·2	27·3	55·2	33·3	96·4

Results are percentages.

Appendix 11.5. Biosocial factors by mode of vaginal delivery and outcome (singleton births in hospital)

	Spontaneous		Breech		Forceps		Embryotomy	
Biosocial factor	Live	Dead	Live	Dead	Live	Dead	Live	Dead
Total numbers	15 352	904	211	145	392	93	0	217
Booking status								
Booked	80·0	32·3	74·9	45·5	54·1	24·7	—	6·0
Unbooked	20·0	67·7	25·1	54·5	45·9	75·3	—	94·0
Ethnic group								
Hausa–Fulani	37·4	77·2	50·7	75·2	67·3	91·4	—	91·7
Other Nigerians	61·7	22·3	47·9	24·1	30·4	8·6	—	8·3
Non-Nigerians	0·6	0·3	0·9	0·7	2·3	0·0	—	0·0
Not stated	0·3	0·1	0·5	0·0	0·0	0·0	—	0·0
Education								
Formal	13·4	4·9	8·1	4·8	11·5	1·1	—	0·0
None	86·6	95·1	91·9	95·2	88·5	98·9	—	100·0
Religion								
Christian	42·4	14·3	35·5	15·9	24·2	5·4	—	4·1
Islam	53·3	83·1	60·2	82·8	71·4	93·5	—	94·5
Others	4·3	2·7	4·3	1·4	4·3	1·1	—	1·4
Residence								
Zaria								
Old City	10·2	9·6	12·3	6·9	13·3	8·6	—	10·6
Sabongari	32·3	16·9	27·0	18·6	18·6	4·3	—	2·8
Tundun Wada	17·4	10·3	19·4	11·0	13·8	7·5	—	1·4
Samaru	17·8	8·7	11·4	7·6	13·8	5·4	—	2·3
Others	9·3	8·0	12·3	8·3	9·9	14·0	—	3·2
Outside Zaria	13·0	46·5	17·5	47·6	30·6	60·2	—	79·7

Results are percentages.

Appendix 11.6. Biosocial factors by non-vaginal deliveries (singleton births in hospital)

Biosocial factors	Caesarean section Live	Caesarean section Dead	Others Live	Others Dead
Total numbers	1613	292	19	130
Booking status				
Booked	51·7	21·9	36·8	10·0
Unbooked	48·3	78·1	63·2	90·0
Ethnic groups				
Hausa–Fulani	69·2	84·6	73·7	90·8
Other Nigerians	30·3	15·4	26·3	8·5
Non-Nigerians	0·4	0·0	0·0	0·8
Not stated	0·1	0·0	0·0	0·0
Education				
Formal	9·1	4·5	5·3	1·5
None	90·9	95·5	94·7	98·5
Religion				
Christian	22·1	12·3	15·8	5·4
Islam	75·7	86·6	84·2	93·8
Others	2·2	1·0	0·0	0·8
Residence				
Zaria				
Old City	11·7	9·9	0·0	6·2
Sabongari	17·5	10·3	26·3	6·2
Tundun Wada	10·4	3·8	0·0	2·3
Samaru	11·3	5·8	5·3	3·8
Others	8·7	6·8	0·0	6·2
Outside Zaria	40·3	63·4	68·4	75·4

Appendix 11.7. Biosocial factors by fetal outcome (singleton births in hospital)

Biosocial factors	Fetal outcome			Perinatal deaths/1000
	Live births	Stillbirths	Neonatal deaths	
Total numbers	17 588	1200	581	92 0
Booking status				
Booked	76·8	22 5	34·6	33·7
Unbooked	23·2	77·5	65·4	242·7
Ethnic group				
Hausa–Fulani	41·2	84·2	76·8	167·4
Other Nigerians	57·9	15·7	22·5	30 4
Non-Nigerians	0·6	0·2	0·5	42·0
Not stated	0·3	0·0	0·2	21·7
Education				
Formal	12·9	3 4	4·5	28·7
None	87·1	96·6	95·5	100·6
Religion				
Christian	40·0	9·6	16·2	28·9
Islam	55·9	88·7	81·6	135·2
Others	4·1	1·8	2·2	44·9
Residence				
Zaria				
Old City	10 4	9·6	8·6	82·7
Sabongari	30 6	11·3	15·8	40·7
Tundun Wada	16·7	5·3	12·0	43·3
Samaru	17·0	5 9	8·8	39·1
Others	9·3	7·2	7·9	74·7
Outside Zaria	16·0	60·8	46·8	262·6

Fetal outcome results are percentages

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12. Maternal mortality

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Summary. There were 238 maternal deaths. Five deaths occurred after delivery among booked women who had no antenatal complications (0·4 deaths per 1000 deliveries); 14 deaths were among booked women who developed complications during pregnancy (3·7 per 1000); and 219 deaths were in the emergency admissions (28·6 per 1000). Bacterial infections, eclampsia, anaemia, haemorrhage and disproportion together with its consequences, were the leading causes. The principal high-risk factors were lack of antenatal care, early teenage pregnancy, high parity and high child mortality rate from previous births. In the emergency admissions the operative delivery rate was 25% in the women who survived and 49% in those who died. In severe eclampsia and in neglected obstructed labour, a high haematocrit (≥0·45) and, to a lesser extent, a low haematocrit (≤0·14) were of ominous significance, mortality rate being 25–60% in such cases compared with <10% in most other obstetric complications. Measures to reduce maternal mortality should aim to lower the proportion of high-risk women (40% at present) and also make it possible for operative deliveries, especially caesarean section, to be performed as soon as the need arises.

Since the early sixties, attention has increasingly been drawn to the high maternal mortality rates of around 10 deaths per 1000 deliveries in many areas in West Africa (Lawson 1962; Waboso 1973; Ojo & Savage 1974; Megafu 1975; Caffrey 1979; Ademowore 1980; Okojie 1980). Cannon & Hartfield (1964), then working under difficult conditions in a rural and semi-urban environment in Western Nigeria, showed how improved standards of health care, together with better organization of basic health services, helped to bring about a reduction in both maternal and fetal mortality and morbidity. Despite the success which Cannon & Hartfield (1964) achieved, they were quick to point out that wherever socio-economic deprivation exists on a large scale and maternal mortality rates are high, the enormous loss of maternal lives cannot be brought under control permanently until living conditions for the general population are improved.

This chapter presents the cold facts about the maternal health situation in the Zaria area and at the same time it attempts to bring to people's notice the underlying human tragedy and suffering. Knowing that the principal conditions associated with maternal death are bacterial infections, anaemia, eclampsia, haemorrhage, disproportion and its consequences, our material was further explored to throw up additional factors which often combined with the obstetric complications in worsening maternal prognosis.

Decision on avoidable factors in maternal death

At the time this material was being collected, it was felt that in the case of the maternal deaths, further information about them was necessary. Therefore, the circumstances surrounding each maternal death were an important part of the discussions at weekly meetings attended by all medical and nursing staff of the Department of Obstetrics and Gynaecology. A consensus was reached as to the clinical causes of death and what avoidable factors there might have been. Such avoidable circumstances were categorized as predominantly due to the patient, the environment, cultural beliefs or to defects in the health services.

An important patient factor was the failure of the women with high-risk pregnancies to report for antenatal care when they should have done so. Another was the fact that some people did not readily submit themselves to emergency operations, preferring instead to withhold consent for operations for as long as possible. For example, rather than give consent for an emergency caesarean section, some of those admitted in early labour with disproportion took their own discharge at that stage, only to return to us later, still undelivered but gravely ill. Cultural practices detrimental to maternal health have already been described (chapter 2). Environmental factors were those connected with difficulties in transportation experienced by women who lived in remote rural areas. In doubtful cases, confirmation was sought from medical social workers and such information enabled us to determine the distance that the woman who died had had to travel to reach the Zaria hospital. Errors of clinical judgement and problems with shortages of, or interruptions to, the supply of piped water, electric power, telecommunications systems, fuel, drugs, linen and other items of essential equipment, all came under avoidable factors within the hospital health services.

Preliminary statistical analysis and social factors

There were 238 maternal deaths (10·5 deaths per 1000 deliveries) of whom 49 died undelivered and 68 gave birth at home before their arrival at hospital. Throughout this text, maternal mortality refers to deaths during pregnancy and up to 42 days afterwards.

Appendices 12.1 and 12.2 show the relation between maternal mortality and antenatal care, address, religion, ethnic group, education, age and parity. The most striking observation is that 219 of the 7654 women who did not receive antenatal care died (28·6 deaths per 1000 deliveries) compared with only 19 of the 15 020 booked delivered women (1·3 deaths per 1000 deliveries).

Of course many women who did not have antenatal care never came to the hospital and were delivered at home. Their number is unknown but must have been at least two to three times the number admitted as an emergency. Even so, the perinatal and maternal mortality among the excluded population of unbooked women is still very much higher than those who received antenatal care.

Another striking observation is that maternal mortality is greatly affected by maternal age. The death rate was highest in girls aged ≤15 years, falling to the lowest level between the ages of 20 and 24 years, then rising again to another peak in the oldest women aged ≥30 years.

Considering just those women who did not receive antenatal care, maternal mortality was still significantly related to both ethnic group ($\chi^2 = 9{\cdot}72$, d.f. = 1, $P<0{\cdot}01$) and religion ($\chi^2 = 7{\cdot}87$, d.f. = 1, $P<0{\cdot}01$) after allowing for maternal age. It is impossible statistically to determine which of these two factors—ethnic group and religion—predicts maternal mortality better, as they are so closely related to each other. Among the unbooked, education, address and parity did not contribute much more to the prediction of maternal mortality after allowing for the other variables, but of course educated mothers rarely failed to receive antenatal care.

Because the distribution of maternal characteristics differed between the booked and unbooked groups (Appendices 12.1 and 12.2), maternal deaths in the two groups will be considered separately.

Maternal mortality in booked patients

There were 19 deaths in the booked group and five of them had no antenatal complications whatsoever and all died after delivery. Two of these five had been discharged within 24 h of normal delivery only to be readmitted 10 days later, when they both died within the first hour of admission, one from severe bronchopneumonia and the other from cerebrovascular accident due to severe postpartum hypertension. Of the other three, one was an anaesthetic death during the repair of a third degree perineal tear; another had severe postpartum haemorrhage and died within minutes before blood for transfusion was available; the third patient in this group had torrential postpartum haemorrhage successfully arrested by hysterectomy, only to succumb to septicaemia later.

Two further deaths were related to HbSS with one dying from pseudotoxaemia (Hendrickse *et al.* 1972) after puerperal sterilization by tubal ligation. The other had active tuberculosis early in the antenatal period. Good progress was being made on drug therapy until pre-eclampsia with sickle cell painful crises developed at 30 weeks, followed 2 weeks later by fatal pericarditis. Being HbSS, her haematocrit, despite multiple transfusions, was still only 0·26.

Nine of the remaining 12 deaths were associated with the following complications: eclampsia (6), post-caesarean section genital sepsis and/or septicaemia (4) and post-caesarean section bronchopneumonia (1). Of these nine women, only one, an eclamptic, died undelivered, two gave birth spontaneously and the remaining six by caesarean section. Spontaneous delivery took place in two eclamptics, one of whom had a twin pregnancy and placental abruption. The indications for caesarean section were severe eclampsia (2), severe eclampsia and twin pregnancy (1), disproportion and intrapartum pre-eclampsia (1), breech presentation and contracted pelvis (1), transverse lie and uterine fibroids (1). In all, six in this group of nine deaths also had mild anaemia (haematocrit 0·24–0·29) in early puerperium as a result of uncorrected blood loss. As is so often the case case in West Africa (Ekwempu 1980), eclampsia was fulminating in five of the six deaths. All five had already had eclamptic fits at home before their arrival in hospital; there had been no warning signs during their weekly antenatal visits.

The remaining three deaths were from acute pyelonephritis in pregnancy (1), pyrexia of unknown origin (1) and postpartum haemorrhage followed by septicaemia after a normal delivery in a patient who had pre-eclampsia.

By the prevailing standards in Zaria, death was reckoned to be unavoidable only in three of the 19 booked deaths. In the rest, the avoidable circumstances were early teenage marriage in three (aged 13–15 years) and defects in our health services in the rest. Of the 19 deaths, 17 were Zaria residents and the other two lived within 50 km. Six had received formal education, although none had had more than primary education. Particularly noteworthy was the fact that in the booked group the death rate was much lower in the women who were healthy throughout pregnancy (five deaths in 11 261 deliveries; 0·44/1000) than in those who developed antenatal complications (14 deaths in 3759 deliveries; 3·7/1000).

Maternal mortality in the unbooked women

General considerations and social characteristics

The unbooked women who died constituted the crux of the problem. Because they were so many (219) and because nearly all presented very late for treatment, they made enormous demands on our limited resources.

Their distribution according to ethnic group, address, religion, age and parity is shown in Appendices 12.1 and 12.2. All the Zaria residents who died and 82% of those whose homes were outside Zaria (range of distances from Zaria, 20–200 km) had access to good roads, by which it is meant that their homes were within 2 km of an all-season road. None of the unbooked women who died had received any formal education.

Table 12.1. Major obstetric and medical complications in 7654 unbooked women of whom 219 died

Obstetric and medical complications	No. of affected women	No. of deaths: One abnormal condition only	No. of deaths: Two or more abnormal conditions
Obstetric			
Genital infection	609	26	28
Eclampsia	390	18	24
Anaemia			
In pregnancy	917	11	50
In puerperium	988	3	48
Haemorrhage			
APH	544	2	21
PPH	391	2	25
Rupture of uterus	177	1	28
Disproportion	1070	0	56
Prolonged labour	988	1	55
Retained placenta	894	2	24
Pre-eclampsia	492	0	12
Postpartum hypertension	559	0	11
Advanced abdominal pregnancy	4	1	0
Non induced abortion	NK	0	2
Medical or surgical			
Sickle cell disease	5	0	1
Specific infections	31	14	4
Other infective conditions	73	0	22
Surgical conditions	NK	3	0
Malignancies	6	1	0
Other non-infective	53	0	7
Traditional surgery			
Gishiri cut	88	1	7
Breast gangrene	7	0	1
Uvulectomy	12	0	1

NK, Not known.

APH, antepartum haemorrhage, PPH, postpartum haemorrhage.

There were avoidable factors related to the patients themselves in 89% of the deaths, to the health services in 53%, to cultural practices in 27% and to the environment in only 9%.

Obstetric and medical complications

Table 12.1 lists the main obstetric and medical complications found in the unbooked women, including those who died. Those cases where death occurred in the presence of a single obstetric or medical complication were in the minority. The more common pattern was death from the combined effect of two or more obstetric complications. For example, while eclampsia was the sole obstetric disease present in 18 deaths, it was accompanied by one other complication in a further 15 deaths, and by two or more other complications in nine. Anaemia was due to the combined effects of malaria and dietary deficiencies of iron and folic acid, sometimes to blood loss and occasionally to sickle cell disease. Where severe anaemia was the only cause of death, the haematocrit ranged from 0·05 to 0·19. Uterine rupture resulted chiefly from disproportion and fetal malpresentations, mostly transverse lie of the fetus.

The surgical conditions associated with maternal deaths were intussusception, volvulus and appendix abscess. Specific infections associated with maternal deaths were typhoid (7), meningitis (5), tetanus (4), hepatitis (1), and amoebiasis (1). Under 'other infective conditions' were 22 fatalities, mostly from pyrexia of unknown origin. Under 'other non-infective' were deaths from peripartal cardiac disease (3), severe bronchial asthma (1), renal failure of unknown cause (1), circulatory overload during intravenous infusion (1) and renal failure from mismatched blood transfusion (1). There were six malignant neoplasms: primary hepatoma (1), malignant trophoblastic disease in remission (4), and goitre (1). The only death was from respiratory obstruction caused by the huge goitre. 'Traditional' surgery describes three procedures. One was the gishiri cut (chapter 2), followed by fatal haemorrhage. Another was burns on the breasts complicated by fatal gangrene and septicaemia. These breast injuries were sustained at home, and followed a traditional form of treatment for breast discomfort in early puerperium. What happened was that a heated metal rod was directly applied to the breasts while it was still very hot. The last procedure was the excision of the uvula by traditional healers complicated by haemorrhage, respiratory infection and septicaemia. This operation, carried out under unhygienic conditions, is for the treatment of sore throat; the practice is widespread but fatalities are apparently rare.

Another matter of interest was a multiple pregnancy rate of one in 19 among the survivors and one in 11 among the deaths. There were 379 twin, nine triplet and two quadruplet pregnancies among the survivors and 14 twin and one triplet pregnancies among the deaths.

The 46 women who died undelivered, were associated with the following conditions: eclampsia (9), severe anaemia with haematocrit of 0·08–0·14 (8), uterine rupture (8), prolonged labour (9), placenta praevia (1), placental abruption (1), haemorrhage from a gishiri cut (2), meningitis (2), pre-eclampsia with anaemia, haematocrit 0·15–0·19 (2), pyrexia of unknown origin (5) and cardiac failure of unknown cause (1).

Of the 1638 women who gave birth at home before arrival in hospital 64 died. The number of survivors and deaths for each complication in this group of emergency admissions was as follows: retained placenta (804, 23), postpartum haemorrhage (181, 16), eclampsia (45, 3), rupture of uterus (14, 2), anaemia in puerperium (530, 27), genital sepsis (223, 21), septicaemia (5, 10), vesicovaginal fistula (10, 3) and secondary PPH (46, 1)

Knowing the principal obstetric and other conditions associated with maternal deaths, analysis was carried a stage further. Attempts were made to determine the relation between each obstetric complication and several other important variables pertinent to local conditions.

Time of death and duration of stay in hospital

Examined in this way, 30 (13·7%) of the deaths took place within the first hour of arrival in hospital, 47 (21·5%) within 1–6 h, 57 (26·0%) within 7–24 h, 55 (25·1%) within 1–7 days and 30 died after more than a week in hospital. However, the pattern varied according to the nature of the underlying obstetric complication. Over 25% of those who died from retained placenta and postpartum haemorrhage but nearly 15% of those with ruptured uterus, anaemia in pregnancy and prolonged labour, died within the first hour in hospital. By contrast, in genital sepsis and anaemia in the puerperium, most deaths (65%) occurred towards the end of the first week of the puerperium. As many as 72% of all who died after embryotomy (13 out of 18) but only 19% of those who died after caesarean section (five out of 27) did so within 24 h after these procedures. This difference in prognosis reflects the difference in severity of the underlying obstetric complications rather than in the operations themselves (see below).

Events of labour and maternal mortality

In the group of emergency admissions, 90% (6719) of the 7481 women who survived and 65% (143) of the 219 who died were in labour when they arrived at hospital for the first time; 25% of the survivors but 44% of those that died were already either in the second or in the third stage of labour. The operative delivery rate for singleton births among the survivors was 24·6% (vaginal breech delivery 2·2%, forceps 3·5%. caesarean section 14·6%, embryotomy 2·7% and other deliveries 1·6%) compared with 53·2% for those who died (vaginal breech delivery 1·9%, forceps 9·5%, caesarean section 16·5%, embryotomy 11·4% and other deliveries 13·9%). The difference in distribution was very significant ($\chi^2 = 188$, d.f. = 5, $P<0{\cdot}001$) Particularly striking were the differences in the proportions of women who required embryotomy and 'other' deliveries between those who died and those who survivied. The term 'other deliveries' throughout this text refers to a total of 144 patients shown in Table 12.2, 113 of whom were abdominal deliveries following uterine rupture. Not shown in Table 12.2 are those women in whom uterine rupture was detected only after vaginal delivery, some in hospital (64) and some at their homes (16). Also not shown are eight others who died undelivered, with uterine rupture present

Maternal age, obstetric complications and mortality

Fig. 12.1 shows that within each of the seven age-groups, the case fatality rate was always less than 10% of all those affected by pre-eclampsia. The same was true for disproportion and prolonged labour. Case fatality rate exceeding 10% occurred in the following groups: early teenage girls with gross anaemia (haematocrit <0·14), eclampsia and postpartum haemorrhage; the over 30s with eclampsia; in all age-groups where uterine rupture took place, that is multiparous mothers aged ≥17 years. In the 17–19 age-group, where mortality associated with rupture of the uterus was highest (37·5%), the number of women affected (three deaths out of eight) was small compared with 6–8 deaths out of 32–74 women affected in the age-groups 20–24, 25–29 and ≥30 years.

Modes of delivery, obstetric complications and mortality

Maternal death rate varied according to the mode of delivery and the nature of the obstetric complications (Fig 12.2). As expected, spontaneous delivery was associated with the lowest

Table 12.2. Mode of 'other delivery' in 144 emergency admissions

		No. of women	
Diagnosis	Mode of delivery	Survivors	Deaths
Rupture of uterus	Laparotomy, repair of ruptured uterus	79	13
Rupture of uterus	Laparotomy, hysterectomy	14	7
Suspected rupture of uterus	Laparotomy followed by spontaneous delivery	1	0
Suspected rupture of uterus	Laparotomy followed by breech delivery with perforation of aftercoming head	1	0
Placenta praevia intrauterine death	Braxton Hicks bipolar podalic version followed by spontaneous delivery	6	0
Obstructed labour	Symphysiotomy	9	2
Hydrocephaly	Spontaneous delivery after aspiration	2	0
Advanced extra-uterine pregnancy	Laparotomy and delivery	3	1
Transverse lie and intrauterine death	Internal version and breech extraction	2	0
Constriction ring	Assisted vaginal delivery	1	0
Others	Not stated	3	0
Total		121	23

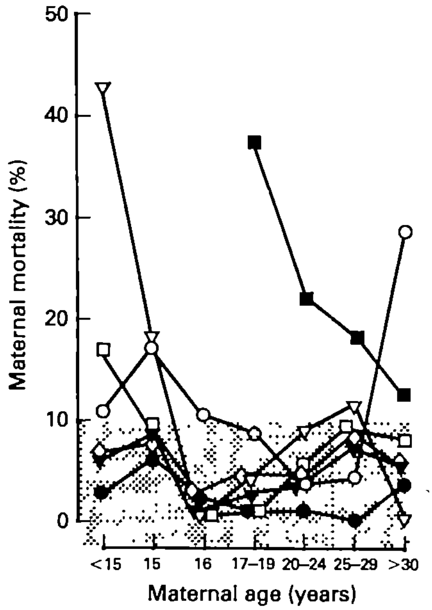

Fig. 12.1. Maternal age, obstetric complications and maternal mortality. ▽ Severe anaemia (haematocrit <0·14); ● pre-eclampsia; ○ eclampsia; ▼ disproportion; ◇ prolonged labour, □ PPH; ■ uterine rupture.

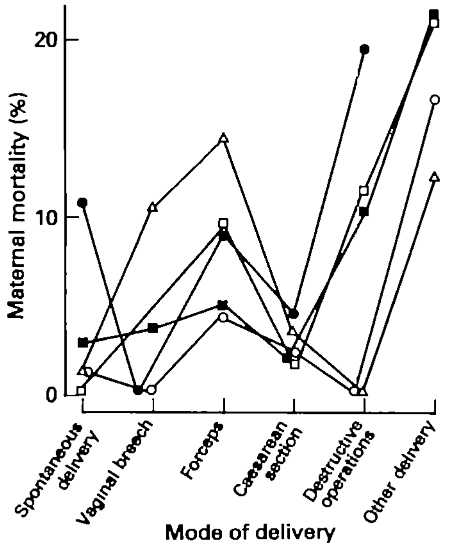

Fig. 12.2. Mode of delivery, obstetric complications and maternal mortality. △ APH; ○ pre-eclampsia; ● eclampsia, □ disproportion; ■ prolonged labour.

case fatality rates (<3%) except among the eclamptics (mortality 11%). Caesarean section performed for whatever reason was always comparatively safe (case fatality <5%). Both embryotomy and other deliveries carried out in the presence of prolonged obstructed labour and eclampsia were associated with the highest case fatality rate of around 20%.

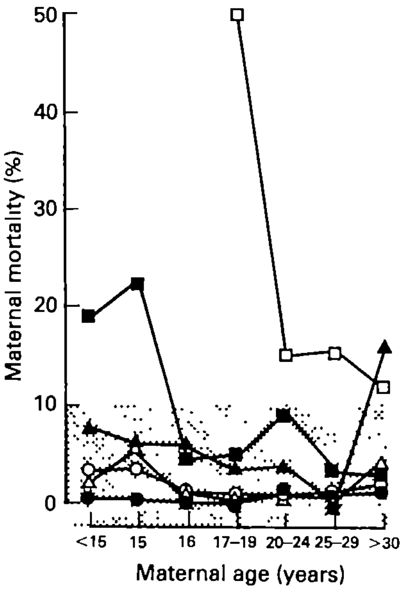

Fig. 12.3. Maternal age, mode of delivery and maternal mortality. ○ spontaneous delivery, ● breech; ▲ forceps; △ caesarean section; ■ embryotomy; □ other deliveries.

Maternal age, mode of delivery and mortality

Fig. 12.3 shows that spontaneous delivery, vaginal breech delivery and caesarean section were comparatively safe as they were all associated with a case fatality rate of under 8%. By contrast, in early teenage girls treated by embryotomy, in the over 30s delivered by forceps (mostly in the presence of eclampsia) and in those who underwent 'other deliveries', irrespective of their age, case fatality rates exceeded 10%.

Maternal haematocrit values and maternal death

Although the aim was to know the venous haematocrit value of every emergency on admission into the labour ward, operational reasons (see discussion) permitted this in only 22% of those who survived and in 55% of those who died.

Haematocrit at delivery (or admission) and time of death. In Fig. 12.4 the haematocrit values on admission were all plotted against the interval between admission to hospital and death. No woman with haematocrit of ≥0·40 died within the first 6 h after admission, even though there

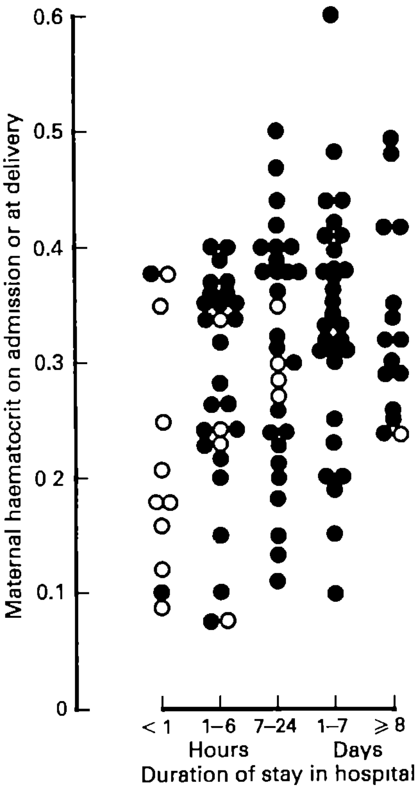

Fig. 12.4. Maternal haematocrit at delivery and interval between admission and death. ○ Born before arrival; ● delivery in hospital.

were among them seven with retained placenta, 21 with ruptured uterus, five with postpartum haemorrhage and one with severe APH. Of those with haematocrit <0·25 and who died within the first 6 h of arrival in hospital, 10 out of the 19 had already given birth at home before arriving in hospital with acute blood loss from retained placenta or postpartum haemorrhage or both combined.

Maternal haematocrit at delivery, obstetric complications and maternal death rate. Table 12.3 relates maternal mortality not only to the haematocrit values at delivery but also to various abnormal conditions. Two groups of women were at the highest risk: those with disproportion, prolonged labour and rupture of uterus in whom the haematocrit value was ⩽0·14, and those with haematocrit values of ⩾0·45, irrespective of the underlying disease As expected, where there had been haemorrhage, maternal haematocrit reading rarely exceeded 0·39. Even so, in women with PPH, maternal death rate was as high as 40% when the haematocrit was 0·35–0·39 compared with between 5% and 16% when the haematocrit was <0·35.

Blood transfusion, haematocrit values and maternal mortality rates. Table 12.4 shows that major operative deliveries had to be performed in the presence of gross maternal anaemia. More importantly, blood transfusion was associated with improved maternal outcome when maternal haematocrit at delivery was <0·20, but not necessarily when the haematocrit was between 0·20 and 0·34, and quite definitely not when the haematocrit was >0·35.

High maternal haematocrit and pregnancy outcome. Eight of the 36 women admitted with a haematocrit of ⩾0·45 died compared with death rates of 4–9% in the other seven haematocrit groups (Table 12·3). Table 12.5 compares the survivors with the deaths among women with high haematocrit values. Antepartum haemorrhage, pre-eclampsia and retained placenta occurred in the survivors but not in those who died. About half of those with eclampsia and ruptured uterus died. All women delivered by caesarean section survived and at the time the operation was performed, the fetus was alive in every case.

Major puerperal complications and maternal deaths. Of all the complications in the puerperium, genital sepsis and anaemia (haematocrit ⩽0·29) were the most frequent, both in the survivors and in the fatalities. Of a total of 7481 survivors, 721 (10%) had anaemia, 339 (4%) had genital sepsis, 216 (3%) had both and 6205 (83%) had neither anaemia nor genital sepsis. Of the 219 deaths, 24 (11%) had anaemia, 27 (12%) had genital sepsis, 27 had both and 141 (65%) had neither. The difference in distribution between the survivors and deaths was very significant ($P<0{\cdot}01$). The other major puerperal complications, together with the number of survivors and number of deaths, were as follows: wound infection (142,9); obstetric fistula (64,12); obstetric palsy (27,2); secondary postpartum haemorrhage (58,3); septicaemia (12,25); and puerperal psychosis (32,2). As well as having the above complications, nearly 62% of the survivors and just over 80% of the deaths (90% in the case of vesicovaginal fistula and palsy) had genital sepsis, anaemia, or both.

Table 12.3. Maternal mortality (%) by haematocrit at delivery and obstetric complications in the unbooked women

Abnormal conditions	Maternal mortality (%) in relation to haematocrit at delivery							
	≤0·14	0·15–0 19	0·20–0·24	0·25–0·29	0·30–0·34	0·35–0·39	0·40–0·44	≥0·45
General anaesthesia	3	3	10	8	8	8	12	23
	(32)	(61)	(83)	(140)	(138)	(171)	(91)	(22)
Eclampsia	0	17	14	9	23	18	25	50
	(1)	(6)	(7)	(11)	(40)	(50)	(28)	(6)
Disproportion	33	0	21	10	8	8	10	29
	(3)	(9)	(30)	(39)	(83)	(119)	(63)	(17)
Prolonged labour	38	0	20	12	10	10	15	25
	(8)	(12)	(30)	(41)	(71)	(89)	(48)	(12)
Uterine rupture	33	0	67	8	8	18	21	57
	(3)	(4)	(6)	(13)	(12)	(17)	(14)	(7)
Antepartum haemorrhage	3	10	3	9	7	17	0	0
	(35)	(50)	(64)	(47)	(30)	(12)	(9)	(1)
Postpartum haemorrhage	7	5	16	9	15	40	0	—
	(15)	(19)	(31)	(43)	(20)	(10)	(5)	(0)
Retained placenta	6	2	6	4	2	10	0	0
	(35)	(86)	(102)	(112)	(45)	(21)	(4)	(3)
No. of all women	122	185	241	331	346	346	170	36
No of deaths	11	10	20	14	19	24	15	8
% deaths	9	5	8	4	5	7	9	22

Results are percentages with the numbers of affected women shown in parentheses.

Table 12.4. Maternal mortality (%) by mode of delivery and blood transfusion in the unbooked women*

Haematocrit at delivery	Spontaneous delivery breech and forceps		Caesarean section		Other deliveries		All deliveries	
	Trans-fused	Not transfused	Trans-fused	Not transfused	Trans-fused	Not transfused	Trans-fused	Not transfused
≤0·14	6	100	7	—	0	—	5·9	100
	(100)	(1)	(15)	(0)	(3)	(0)	(118)	(1)
0·15–0·19	1	29	10	—	0	—	1·8	28·6
	(142)	(14)	(20)	(0)	(6)	(0)	(168)	(14)
0·20–0·24	6	6	7	18	22	0	7·0	7·6
	(133)	(54)	(30)	(11)	(9)	(1)	(172)	(66)
0·25–0·29	1	2	2	0	18	0	2·8	1·9
	(118)	(139)	(41)	(12)	(17)	(3)	(176)	(154)
0·30–0·34	2	2	12	3	11	30	7·6	3 6
	(40)	(207)	(33)	(34)	(19)	(10)	(92)	(251)
0·35–0 39	18	3	4	2	13	21	8·8	4·1
	(17)	(183)	(51)	(44)	(23)	(19)	(91)	(246)
0·40–0·44	25	6	5	3	20	13	13·3	5 6
	(8)	(81)	(22)	(35)	(15)	(8)	(45)	(124)
≥0·45	33	13	0	0	43	50	33·3	12 5
	(3)	(15)	(2)	(7)	(7)	(2)	(12)	(24)
Not recorded	3	0·5	1	0·5	11	3	3·2	0 6
	(623)	(4339)	(350)	(379)	(119)	(104)	(1092)	(4822)

*Excludes data on women who died undelivered.

Results are percentages with the numbers of affected women shown in parentheses.

Table 12.5. Maternal outcome and intrauterine fetal death by obstetric complications and mode of delivery (unbooked women with haematocrit of ≥0·45 only)

Factors	Total	Survivors	Deaths
Total no	36	28	8
Obstetric complications			
Antepartum haemorrhage	1	1	0
Pre-eclampsia	4	4	0
Postpartum haemorrhage	0	0	0
Retained placenta	3	3	0
Eclampsia	6	3	3
Disproportion	17	12	5
Prolonged labour	12	9	3
Uterine rupture	7	3	4
Genital sepsis	5	1	4
Treatments			
General anaesthesia	22	17	5
Blood transfusion	12	7	5
Mode of delivery			
Spontaneous delivery	12 (6)	10 (5)	2 (1)
Vaginal breech	1 (1)	0 (0)	1 (1)
Forceps	5 (1)	4 (0)	1 (1)
Caesarean section	9 (0)	9 (0)	0 (0)
Destructive operations	2 (2)	1 (1)	1 (1)
Laparotomy for ruptured uterus	7 (6)	4 (3)	3 (3)

Results are numbers of women, with numbers of intrauterine fetal deaths on admission shown in parentheses

Mode of delivery, genital sepsis, puerperal anaemia and mortality

Table 12.6 shows that among those admitted to hospital after home delivery, whether they eventually survived or died, the risk of puerperal anaemia and genital sepsis was high: more than 40% of them had either anaemia or genital sepsis or both combined. Following hospital delivery, however, the prevalence of anaemia and genital sepsis varied depending on the mode of delivery between 4% and 43% in those who survived and between 20% and 76% in those who died.

Fetal outcome

Table 12.7 shows the fetal outcome in the women who died and in those who survived: fetal survival for hospital and home births was similar in the surviving women ($\chi^2 = 4{\cdot}8$, d.f. = 2, $P = 0{\cdot}09$), whereas in the women who died, the proportion of stillbirths in hospital deliveries was 2·5 times greater than among home births ($\chi^2 = 38$, d.f. = 2, $P<0{\cdot}01$). Table 12.8 shows that 38% of babies born to the women who died were normal-birthweight babies who had all died *in utero* before arrival at the hospital. Only 8% of the babies of the surviving women were in that category. A total of 2317 babies, including those that were motherless, were weighed on discharge from hospital; 39% of the babies of the surviving mothers and 40% of the motherless babies weighed ≤2·5 kg at that time.

Past obstetric history and maternal mortality

Information about previous children was available from 7006 of the surviving women and 202 of those who died. The women who survived

Table 12.6. Puerperal anaemia, genital sepsis, mode of delivery and maternal deaths (unbooked women)

	No. of women		% with anaemia, genital sepsis, or both	
Mode of delivery	Survivors	Deaths	Survivors	Deaths
Home births*	1574	64	40	52
Hospital births				
Spontaneous delivery	4079	24	4	76
Vaginal breech	197	3	8	33
Forceps	257	15	14	20
Caesarean section	1049	27	33	52
Embryotomy	203	18	31	50
Other deliveries	121	23	43	66
Major operations				
Repair of ruptured uterus	113	18	51	72
Hysterectomy	30	5	57	60

*Born before arrival at hospital

Table 12.7. Maternal and fetal outcome by place of birth (unbooked women, singleton and multiple births combined)

	Survivors			Maternal deaths		
Fetal outcome	Number	% of group	% of total	Number	% of group	% of total
Hospital births						
Live birth	4696	75·3	59·6	28	23·5	15·0
IUD on admission	838	13·4	10·6	66	55·5	35·2
IUD after admission	224	3·6	2·8	10	8·4	5·3
Neonatal death	477	7·7	6·1	15	12·6	8·0
Home births*						
Live birth	1226	74·6	15·6	47	69·1	25·1
Stillbirths	266	16·2	3·4	16	23·5	8·5
Neonatal death	152	9·2	1·9	5	7·4	2·7

*Born before arrival at hospital
IUD, Intrauterine death

Table 12.8. Fetal birthweight by fetal outcome in babies of surviving women and in motherless babies

Fetal birth-weight (kg)	Fetal outcome	Babies of surviving women	Motherless babies
≤2·5	Live	759 (13·5)	9 (8·7)
	IUD on admission	286 (5·1)	16 (15·5)
	IUD after admission	79 (1·4)	4 (3·9)
	Neonatal death	169 (3·0)	9 (8·7)
>2·5	Live	3584 (63·9)	16 (15·5)
	IUD on admission	451 (8·0)	39 (37·9)
	IUD after admission	98 (1·7)	5 (4·9)
	Neonatal death	187 (3·3)	5 (4·9)
Total		5613 (100·0)	103 (100·0)

Results are numbers, with percentages in parentheses.
IUD, Intrauterine death

had a total of 15 788 children from previous births (parity 0–16) and the women who died had a total of 505 children (parity 0–13), giving a mean number of 2·25 children per woman who survived and 2·50 for those who died. However, the proportion of surviving children was 71% (1·61 per woman) for the surviving women and only 58% (1·44 per woman) for the dead women.

Fig. 12.5 and Table 12.9 present the proportion of live children from previous births against maternal mortality rate at each parity group. Maternal mortality rate rose as child survival worsened, particularly in those with seven or more previous births.

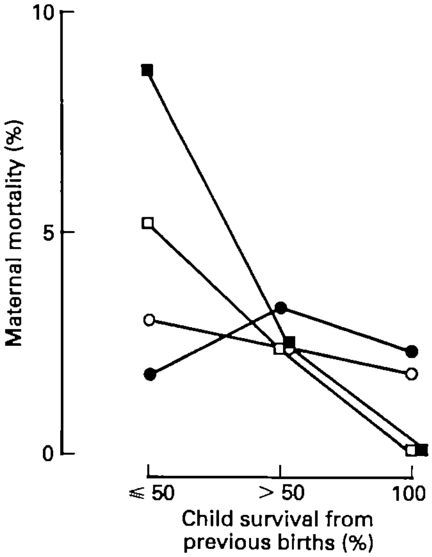

Fig. 12.5. Child survival, previous births (○ 1–2, ● 3–6; □ 7–9; ■ ≥10) and maternal mortality.

Discussion

The statistics reported here display a maternal death rate which is high even by Third World standards (Makokha 1980; Mtimavalye *et al.* 1980; Chi *et al.* 1981; MacPherson 1981). Too many women died because they reported for treatment when their illness had reached an advanced stage. The nature of the obstetric complications, the frequent resort to embryotomy,

Table 12.9. Child mortality, previous births and maternal death rate (unbooked women)

	% of children alive from previous births								
	≤50			>50			100		
		Maternal deaths			Maternal deaths			Maternal deaths	
Parity	Total no.	*n*	%	Total no.	*n*	%	Total no	*n*	%
1–2	506	15	3·0	—	—	—	1055	20	1·9
3–6	509	9	1·8	599	20	3·3	654	16	2·4
7–9	192	10	5·2	311	7	2·3	57	0	0·0
≥10	116	10	8·6	84	2	2·4	6	0	0·0

the large proportion of women dying within the first 6 h of arrival in hospital, and the high stillbirth rate among babies of normal birthweight, all attest to this fact.

Data analysis on maternal mortality in Zaria is compounded by there being more than one obstetric or medical cause for most maternal deaths. Faced with this problem, the practice in many places is to ascribe death to one principal or major cause, regarding all others as merely secondary or contributory. This system of classification is difficult to justify in Zaria where, for cultural and religious reasons, autopsies are not performed. In presenting the principal diseases or complications associated with maternal mortality, the system adopted both here and in a previous report (Harrison 1980) is one which reflects all the major circumstances surrounding each maternal death. In this way, the contribution each obstetric complication made to the overall spectrum of maternal death becomes clearer, a point borne out by the analysis of the relation between maternal haematocrit levels and other obstetric complications (Table 12.3).

An intriguing finding is the association of high maternal haematocrit level with poor maternal prognosis in eclampsia. Koller (1982) argued that by its effect in increasing blood viscosity and hence causing placental infarcts, a high maternal haemoglobin level is associated with intrauterine fetal death. In chapter 11, fetal outcome was shown to be best when maternal haematocrit level at delivery was between 0·30 and 0·40, and that at higher haematocrit levels, the risk of low birthweight and perinatal death increased. Apparently the relation between maternal haematocrit level and pregnancy outcome does not end there. According to this report, there are at least two obstetric conditions—anaemia and eclampsia—where maternal haematocrit level gives some indication of the severity of the underlying condition. In anaemia, maternal risk increases as the haematocrit value drops, whereas in eclampsia, mortality rises as the haematocrit level rises above 0·40. A very high haematocrit level was also a feature of prolonged obstructed labour, especially when this culminated in uterine rupture (Table 12.5). In this case, haemoconcentration from dehydration was the probable cause, whereas in eclampsia, the mechanism for the rise in haematocrit was volume depletion through vasoconstriction and altered vascular permeability (Gallery *et al.* 1979). In either case, resort to delivery by caesarean section was apparently safer than any other form of delivery (Table 12.5). But such a result was principally due to selection. In women with less advanced disease, the fetus was still alive, and so delivery by caesarean section was favoured but in those with more severe disease, the fetus was often already dead *in utero*, and so the practice was to avoid caesarean section.

There is no doubt that fetal and maternal survival are strongly linked. For example, in this series, even among the women who failed to receive antenatal care, the survivors achieved better fetal results than those who died. This connection between maternal and fetal outcome was also evident when child survival rates from previous births were compared between the survivors and those who died. Again, the survivors had a marked advantage over those who died. Indeed in the situation in Zaria, there is some justification for regarding a high child mortality rate by itself as a maternal risk factor, perhaps on a par with high parity and early teenage pregnancy. Of course all these three reproductive patterns are closely linked and they are indicative of the serious defects in the living conditions in the area.

As many as 80% of deaths occurred in women who had reasonable access to health care as they lived less than 2 km from a main road. This was an unexpected finding and it carries wider implications. For a full appreciation of what these implications are, it is necessary first of all to recall that the illness from which the emergency admissions died always started at their homes. When they realized that expert intervention was required and because road communication for them was comparatively easy, they eventually reached hospital where they died. For those living in remote areas without access to hospital (perhaps 60% of the population) the deaths from complications needing operative treatment are almost certainly greater than the hospital statistics would suggest. On the other hand, it can also be argued that in places such as Zaria, where vital statistics for the whole area are not kept, it is not possible to say with confidence whether maternal mortality rates among the rural dwellers were any higher than those observed at the hospital. There is another side to this argument. Most of those with homes outside Zaria, whether they live close by or far from a main road, belong to the same sociocultural–ethnic group (Murphy & Baba Tukur 1981). Their attitudes to life are the same (Lister 1980) and so it is very likely that the obstetric conditions needing operative intervention, such as obstructed labour and eclampsia, will arise just as often, and that in the absence of effective treatment, the mortality among the rural dwellers in remote areas must be very high indeed. Exactly how many perish in this way is not known, but the fact that each year there were nearly 300 fresh cases of vesicovaginal fistula attending the gynaecological clinic in Zaria, many from the rural background, gives some indication of the scale of maternal morbidity and mortality among the rural dwellers.

A recent report of 20–24 maternal pregnancy-related deaths per 1000 women of childbearing age in certain isolated villages in Gambia, West Africa (Lamb *et al* 1984) nearly match the maternal mortality rate in the unbooked women in our Zaria study, 29 per 1000, these rates are between 2 and 20 times the rates commonly reported from urban hospitals in developing countries. It may well be that the relatively 'low' maternal mortality rates from urban centres grossly underestimate the magnitude of the problem at least in the poverty stricken parts of West Africa. All this is very reminiscent of the situation in 18th century rural England with its mortality rates of 24–29 maternal deaths per 1000 baptisms (Dobbie 1982).

As in many societies, maternal mortality in Zaria has now been shown to vary with maternal age. Maternal mortality, high among the early teenage mothers, fell to the lowest level between the ages of 20 and 29 years, and rose again with advancing age. This age effect on maternal survival was quite pronounced in eclampsia, severe anaemia, prolonged labour, postpartum haemorrhage, uterine rupture and even after certain operative deliveries. In most cases, except eclampsia in the over 30s, it was the teenage girl who came out worst of all. Exactly why this is so is not clear from the analysis, but it may be a consequence of one of the important traditional customs in the area. There is a strongly held belief that home delivery is best for young teenage girls. So it would seem likely that when things went wrong during labour, people were slow to seek expert help whenever teenage expectant mothers were the ones affected.

Complications of early pregnancy featured very little in these Zaria maternal deaths partly because of the selective nature of this survey and partly because of people's attitude towards health care. Although each year about 600 women with incomplete abortion and 90 with ectopic gestation were being treated, the vast majority, having been discharged early, were lost to follow-up. Attitudes to child-bearing remain very traditional among most people in Zaria. Only a tiny minority practise effective contraception, and pregnancy termination—except for medical reasons—is seldom resorted to. Therefore, death from criminal abortion, which is rampant in many Third World cities, did not occur in Zaria during the period of this survey. As many as 88% of those who reported to hospital for antenatal care did so for the first time in the second half of pregnancy. Therefore, in the Zaria area, fatalities from early pregnancy complications, such as spontaneous incomplete abortion and molar pregnancy, might well have taken place outside hospital without attracting much notice.

Regarding the motherless babies, the results presented here would suggest that while these babies were in hospital, the support given to them was probably no worse than that received by the other babies. The proportion that weighed ≤2·50 kg on discharge was the same for both the motherless babies and the rest. The existing infant welfare clinic and a home for motherless babies in Zaria both served to complement whatever care these babies received at their homes.

Attention must now be turned to the events in the hospital itself and to some other results of this study. These include the high prevalence of bacterial infections, the circumstances surrounding blood transfusion, and also the predictive value of maternal haematocrit. Judging from the maternal haematocrit values at delivery, there is no doubt that many emergency admissions were in poor health. They were clearly high operative risks at the time they were subjected to major operative procedures. Thirteen per cent of those who had general anaesthesia, 10% of those subjected to either repair of ruptured uterus or hysterectomy and 30% with retained placenta, some of whom subsequently needed manual removal of the placenta, arrived at hospital with venous haematocrit values <0·20. Among the survivors were women admitted in obstructed labour with haematocrit of 0·09, eclamptics with haematocrit of 0·13, and those who, despite a haematocrit of only 0·07, had to have manual removal of placenta carried out shortly after admission.

Under these circumstances, blood transfusion played a crucial role in the management of the emergency admissions in Zaria, with as many as 24% of the survivors and 48% of those who died receiving transfusion. However, there were problems. Shortage of donor blood was not one of them but delay in getting transfusion started was. The major constraints were faults in the transportation and in the telecommunication systems and frequent interruptions to the electric power supply. Occasionally, the hospital ran out of supplies of very basic items such as blood giving sets, suitable serum needles and intravenous cannulae. Blood that was not cross-matched was hardly ever transfused, although the use of blood cross-matched for less than 2 h was commonplace. In spite of these shortcomings, there is no doubt that blood transfusion proved life-saving when used to raise the circulating haemoglobin level quickly in patients found to be grossly anaemic during labour or shortly afterwards (Harrison 1982). However, there is no ready explanation as to why, when maternal haematocrit was between 0·20 and 0·39, blood transfusion failed to show the same sort of advantage as it did when the haematocrit was <0·20. In the case of women with high haematocrits (≥0·45), the increased risks they ran when they were transfused, as opposed to when they were not transfused (Fig. 12.6) would suggest that the use of blood transfusion was inappropriate, or that such patients were being over-transfused, or that insufficient attention was being paid to coexisting biochemical disturbances. It may also be that those who were transfused had the more severe disease. If so, the poor results they had may be due not so much to the transfusion itself as to the severity of the underlying disease, be it eclampsia, prolonged obstructed labour or rupture of the uterus. Whatever the explanation, there is the whole question of body fluid replacement during emergency operative procedures in these volume-depleted patients with high haematocrit and possibly metabolic acidosis (Akinkugbe *et al.* 1977). All these and other issues about these patients deserve further study. Meanwhile, an important step towards reducing maternal mortality in places such as Zaria would be the installation of a microhaematocrit centrifuge in the labour ward itself, so that the haematocrit value of all emergency admissions in labour could be determined on the spot and the results made known promptly.

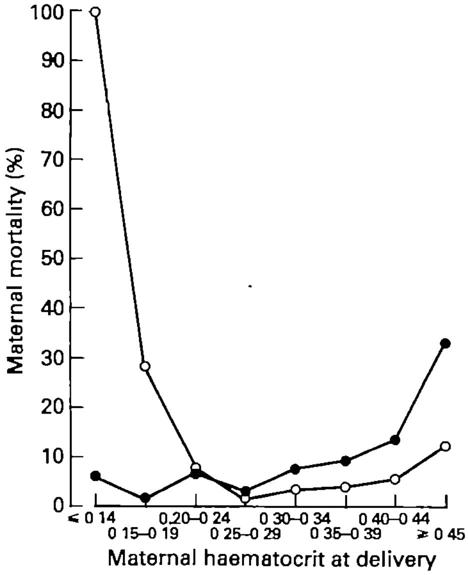

Fig. 12.6. Maternal haematocrit at delivery, blood transfusion and maternal mortality ● Transfused: ○ not transfused

Further cause for concern in Zaria was the mortality associated with bacterial infection in the puerperium. Both booked and emergency admissions who died were almost equally affected. Faults in the hospital environment and improper hygiene were chiefly the cause (see chapter 2).

It is obvious that the majority of the obstetric and medical complications associated with maternal mortality, related as they were to the prevailing social attitudes and severe deprivation, were largely preventable. However, the fact remains that the fundamental problem of maternal health in the Zaria area is the existence of an exceedingly large proportion of high-risk women—early teenage primigravidae, high parity, and lack of antenatal care—making up 40% of the survey population compared with only 2%, for example, in Australia (Lumley 1980). If maternal mortality is to fall, the long-term need is a reduction in the proportion of women with these three high-risk factors. The way to do so is to improve living standards (Chalmers 1980), never neglecting universal formal education in the process (chapter 3). In the short-term, however, it should be possible to improve the health of the pregnant women through antenatal care, and then gain acceptance in the population so that operative deliveries, especially caesarean sections, can be performed as soon as the need arises.

Appendix 12.1. Maternal mortality by social factors and booking status

	Maternal mortality rate/1000											
	Unbooked				Booked				Not stated			
Social factors	Hausa–Fulani	Other Nigerians	Others	Not stated	Hausa–Fulani	Other Nigerians	Others	Not stated	Hausa–Fulani	Other Nigerians	Others	Not stated
Residence												
Zaria	27·8	7·5	0·0	0·0	1·8	1·0	0·0	0·0	0·0	0·0	—	—
	(2593)	(666)	(8)	(16)	(3890)	(9989)	(105)	(25)	(15)	(21)	(0)	(0)
Outside Zaria	35·2	15·0	0·0	0·0	3·9	0·0	0·0	—	0·0	—	—	—
	(3778)	(200)	(7)	(2)	(517)	(335)	(7)	(0)	(11)	(0)	(0)	(0)
Not stated	19·5	0·0	—	0·0	0·0	0·0	—	0·0	0·0	—	—	0·0
	(308)	(47)	(0)	(29)	(78)	(69)	(0)	(5)	(2)	(0)	(0)	(2)
Religion												
Christian	0·0	8·9	0·0	0·0	0·0	1·0	0·0	0·0	—	0·0	—	—
	(25)	(562)	(4)	(23)	(72)	(7028)	(40)	(16)	(0)	(11)	(0)	(0)
Islam	31·9	11·7	0·0	0·0	2·1	0·7	0·0	0·0	0·0	0·0	—	0·0
	(6617)	(256)	(9)	(10)	(4365)	(2773)	(27)	(5)	(26)	(9)	(0)	(1)
Others	—	0·0	—	—	—	0·0	0·0	—	—	—	—	—
	(0)	(5)	(0)	(0)	(0)	(12)	(9)	(0)	(0)	(0)	(0)	(0)
Not stated	0·0	0·0	0·0	0·0	0·0	1·7	0·0	0·0	0·0	0·0	—	0·0
	(37)	(90)	(2)	(14)	(48)	(580)	(36)	(9)	(2)	(1)	(0)	(1)
Formal education												
Education	0·0	0·0	0·0	—	9·6	2·3	0·0	0·0	—	0·0	—	—
	(6)	(50)	(3)	(0)	(104)	(2193)	(76)	(3)	(0)	(2)	(0)	(0)
None	31·8	9·4	0·0	0·0	1·8	0·6	0·0	0·0	0·0	0·0	—	0·0
	(6636)	(849)	(12)	(47)	(4347)	(8093)	(29)	(27)	(28)	(19)	(0)	(2)
Not stated	0·0	0·0	—	—	0·0	0·0	0·0	—	—	—	—	—
	(37)	(14)	(0)	(0)	(34)	(107)	(7)	(0)	(0)	(0)	(0)	(0)
All deaths	211	8	0	0	9	10	0	0	0	0	0	0
All deliveries	6679	913	15	47	4485	10 393	112	30	28	21	0	2

Numbers of deliveries are shown in parentheses

Appendix 12.2. Maternal mortality (deaths per 1000 deliveries) by age, parity and booking status

Maternal age (years)	All deliveries				All primigravidae				All multigravidae				Parity ≥5			
	Un-booked	Booked	Not stated	Total	Un-booked	Booked	Not stated	Total	Un-booked	Booked	Not stated	Total	Un-booked	Booked	Not stated	Total
<15	56·1	10·5	—	37·8	56·7	10·8	—	38·5	0·0	0·0	0·0	0·0	—	—	—	—
15	71·3	2·1	0·0	39·7	73·6	2·4	0·0	41·9	32·2	0·0	—	12·7	—	—	—	—
16	32·0	0·0	0·0	14·3	32·9	0·0	0·0	14·6	28·2	0·0	—	12·7	—	—	—	—
17–19	20·8	0·9	0·0	7·6	21·0	0·0	0·0	8·0	20·5	1·8	0·0	7.1	0·0	0·0	—	0·0
20–24	19·6	1·0	0·0	5·8	11·8	1·1	0·0	4·8	22·5	1·0	0·0	5·9	22·0	0·0	—	9·7
25–29	24·9	1·3	0·0	7·4	17·5	0·0	0·0	6·1	25·0	1·4	0·0	7·3	27·1	1·5	0·0	11·6
≥30	36·8	1·6	0·0	15·1	19·2	0·0	—	10·1	37·8	1·7	0·0	15·3	45·3	1·5	0·0	20·1
Not recorded	1·7	0·0	0·0	1·1	0·0	0·0	—	0·0	2·4	0·0	0·0	1·6	0·0	0·0	—	0·0
Total no. of deliveries	7654*	15 020*	51*	22 725*	2767	3543	13	6323	4804	11 460	36	16 300	1693	2174	12	3879
Total no. of deaths	219	19	0	238	92	4	0	96	125	15	0	140	59	3	0	62
Deaths per 1000 deliveries	28·6	1·3	—	10·5	33·2	1·1	—	15·2	26·0	1·3	0·0	8·6	34·8	1·4	0·0	16·0

*Data on total deliveries include those on 102 mothers (83 unbooked with two deaths, 17 booked and two not stated) with missing parities

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13. Conclusions

It must be obvious from this study that unsuccessful child-bearing in an area like Northern Nigeria is due overwhelmingly to socioeconomic and cultural features rather than to existing deficiencies in the maternity services.

Large numbers of women are born into a cycle of deprivation where they will remain uneducated; where their religion and culture encourages child marriage so that they may begin child-bearing while still children themselves, and where they are systematically neglected both physically and emotionally. Moreover, they may be denied access to effective medical care when they need it, and the consequent damage by neglect is compounded by inappropriate and exceedingly harmful traditional medicine.

It is not easy to see how this cycle may be broken but it was apparent that women born into better circumstances, and educated, did not marry before they were mature, were better grown and more healthy, and sought professional advice in pregnancy. So that while the deprived group and their infants suffered the consequences of antenatal neglect—no malaria prophylaxis, unchecked hypertensive complications, anaemia—neglect in labour leading often to obstruction, uterine rupture, obstetric fistula and fetal death; and postpartum neglect leading to blood loss and infection, the better informed women who had professional care were able to avoid these problems.

The late sequelae of neglect put an unreasonable stress on the maternity services and if those services sometimes proved to be deficient that was often because they were overwhelmed by the load of essentially self-inflicted obstetric casualties.

Until there is a fundamental social change, beginning with universal formal education, emergency obstetric care must continue to make the best of an unsatisfactory situation. To that end, the survey has provided some useful lessons. During pregnancy in young teenagers, iron and folic acid supplements combined with malarial chemoprophylaxis prevents maternal anaemia and promotes fetal growth. The same regimens, by enhancing maternal growth, also reduce cephalopelvic disproportion and cut down on the need for operative deliveries.

Monitoring of haematocrit on the one hand for anaemia and on the other hand as an indication of volume-depletion due to either pre-eclampsia or dehydration is absolutely vital. The treatments needed are very different and inappropriate action may be fatal.

Turning to perinatal deaths, the largest proportion consisted of normally formed stillbirths of normal birthweight, who died before admission to hospital. Both neonatal deaths and low birthweight perinatal deaths occupied a subordinate position, and congenital malformations were of little consequence. Thus, reducing intra-uterine deaths of normal birthweight babies is an area of priority, and to this end the need is for prompt and bold operative interference, especially caesarean section, where indicated.

Lastly, there can be no doubt whatsoever that reducing maternal deaths is the *real* priority. Here, the health services and those who manage them must assume the critical role of demonstrating to a sceptical public that the hospital can provide excellent life-saving treatment and should be patronized by everybody.

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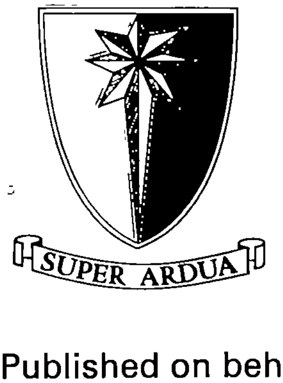

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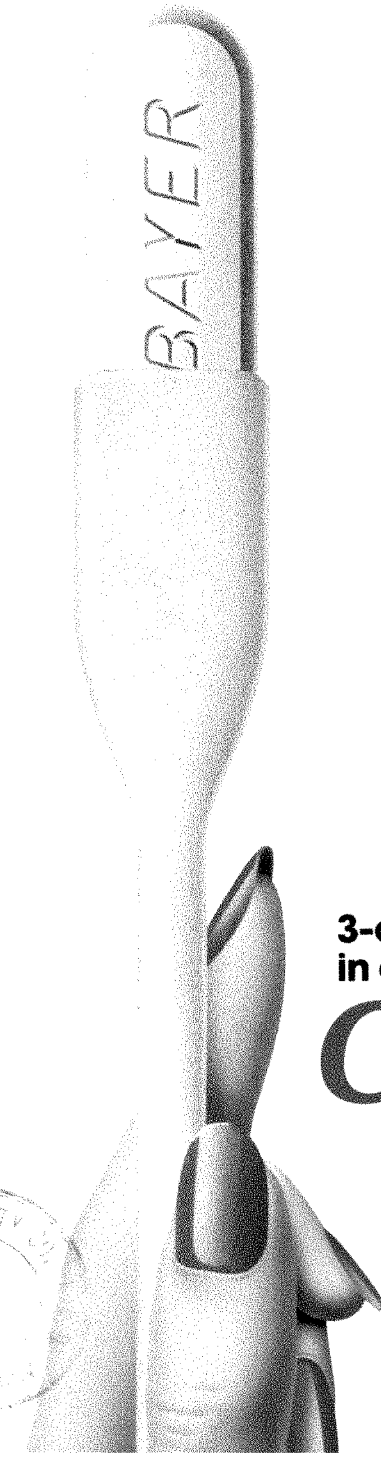

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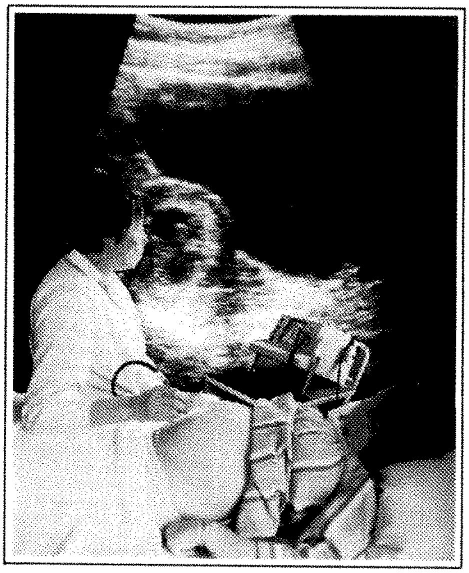

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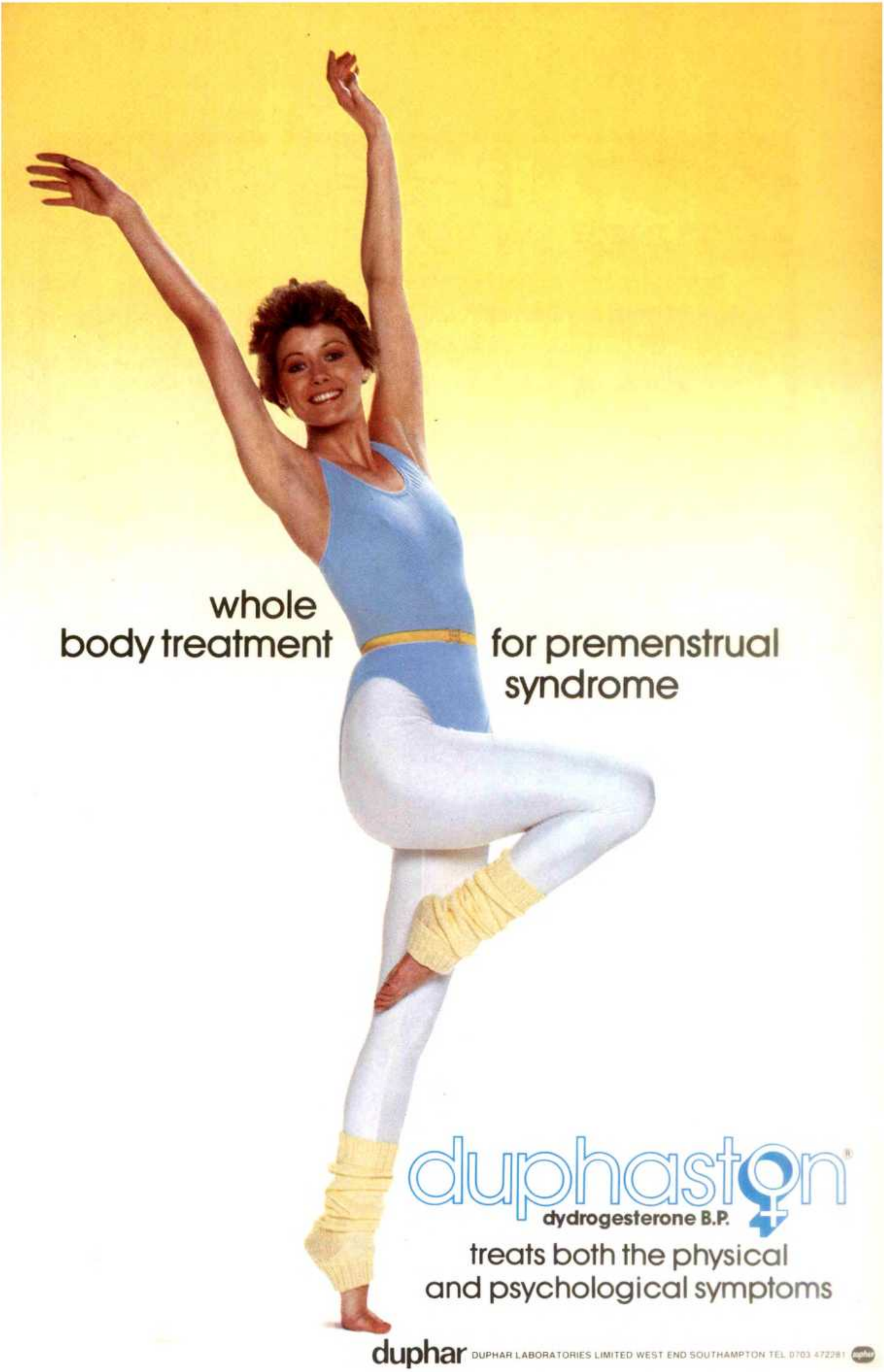

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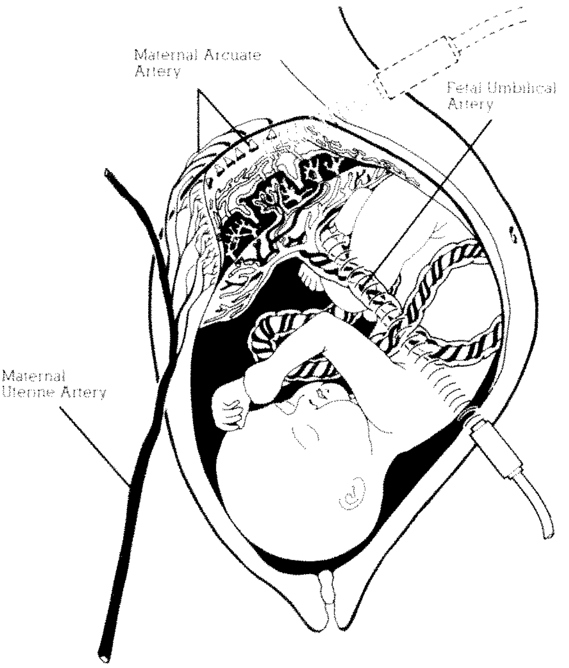

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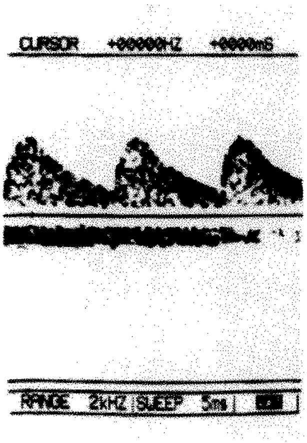

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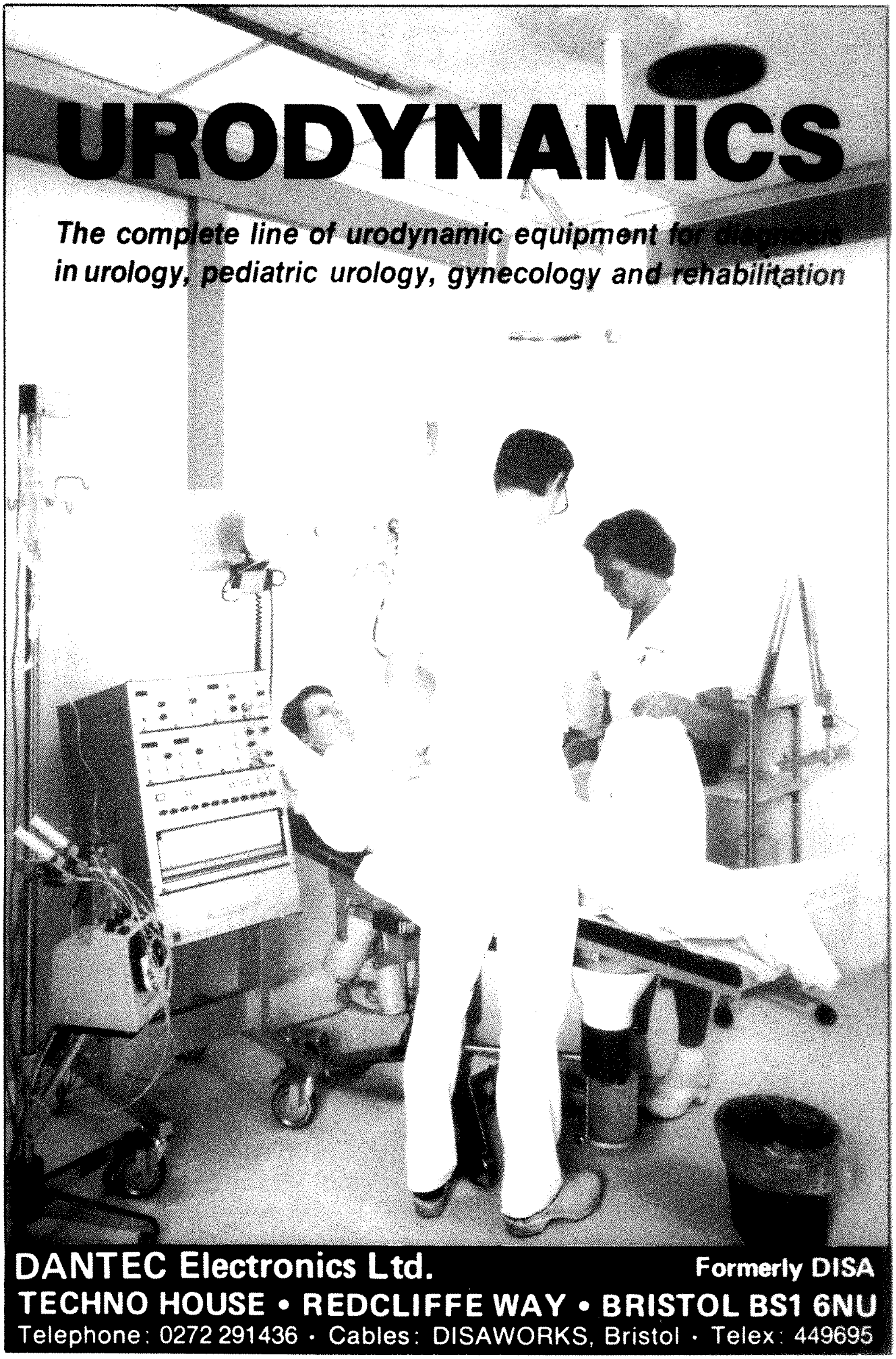

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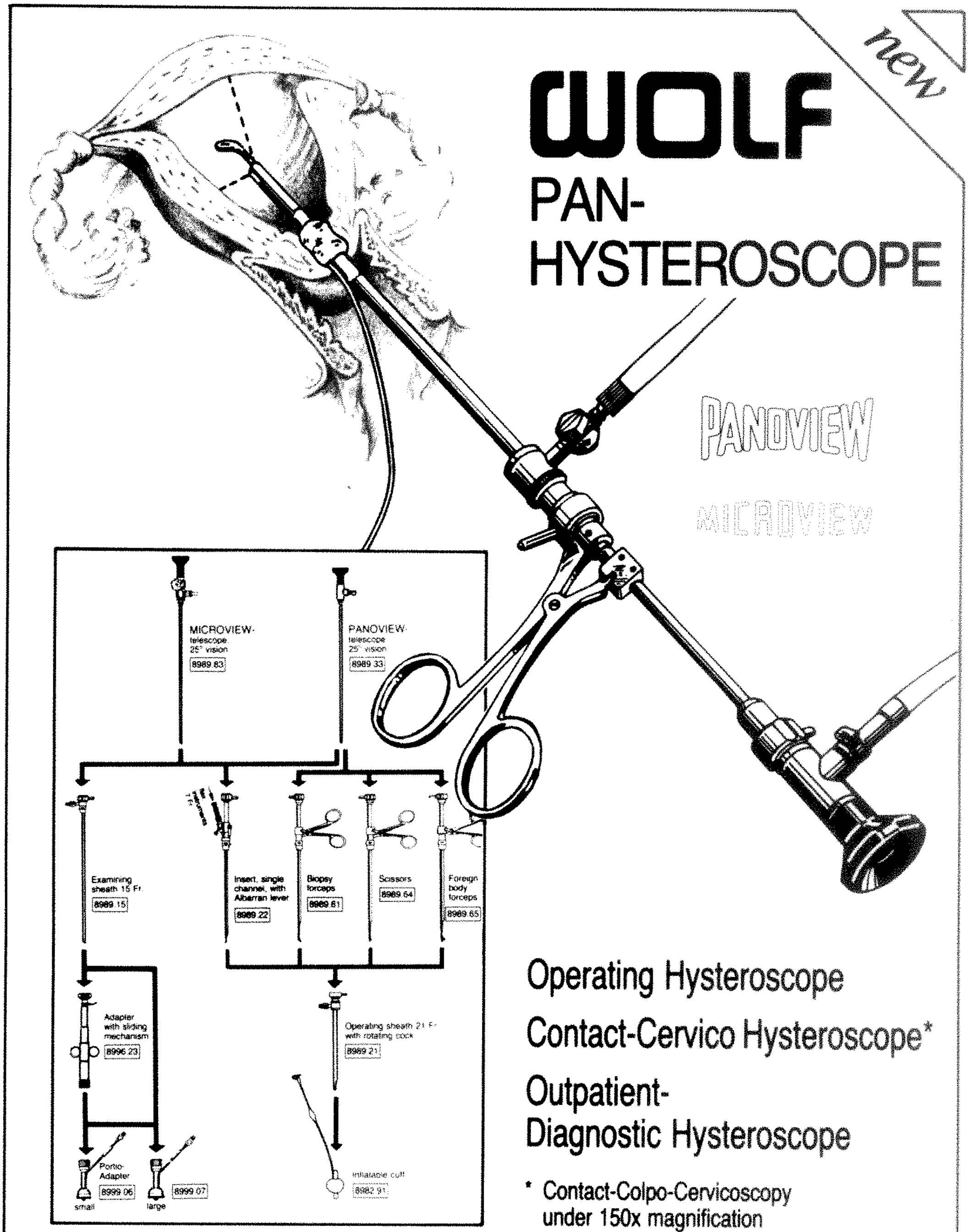
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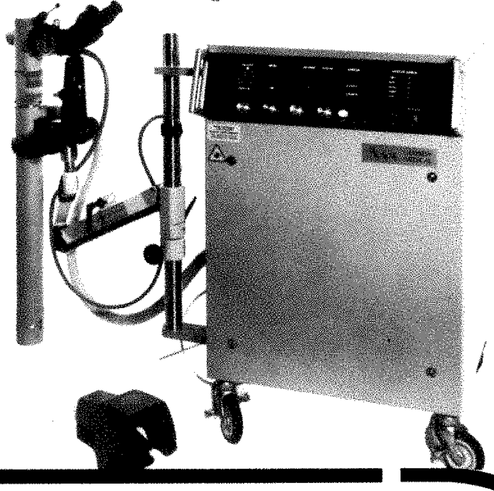

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COMMENTARY

Enquiry into perinatal death

Enquiry into perinatal death within Britain has taken many forms since 1917 when 'the mortalities of birth, infancy and childhood' were examined formally on behalf of the National Health Insurance Medical Research Committee (Chalmers *et al* 1917). All the various approaches which have been used since then, however, have shared the common aim of identifying means through which further reductions in the risks of fetal and infant mortality might be secured.

Methods of enquiry into perinatal death have ranged from the regular, informal, clinical reviews of individual cases which have become more or less universal within British maternity hospitals (Enkin & Chalmers 1980), through the more formal assembly of uncontrolled case series, either based on hospital case loads, or on geographically defined populations (like the Wessex Perinatal Mortality Survey reported on p. 550 of this issue); to those enquiries which have made formal comparisons between the characteristics of cases who died and those of controls who survived. Enquiries into perinatal death which have used control data have done so either within the framework of case-control studies, as in Leicestershire (MacVicar 1980, Clarke 1982); or through specially mounted epidemiological surveys based on all births, like those mounted in Aberdeen (Baird & Wyper 1941; Baird *et al.* 1953, 1954) and at national level (Butler & Bonham 1963; Butler & Alberman 1969); or by using routinely collected birth and death statistics, like the analyses reported by Edouard & Alberman (1980), Macfarlane & Mugford (1984) and Alberman in this issue (p. 559). It is against the background of this tradition of enquiry into perinatal death and the successful implementation of a national system of enquiry into maternal deaths that there have been calls for an 'ongoing and formal enquiry process' into perinatal death throughout Britain.

Any such enquiry process must obviously be endorsed widely if it is to be implemented successfully. Although there have been many official statements of support for the principle of an ongoing, nationwide, formal enquiry into perinatal death, it has proved difficult to reach agreement about the form this should take (Chalmers 1984). In 1980, a study group involving many of the interested parties was organized under the auspices of the Royal College of Obstetricians and Gynaecologists, both so that existing experience of differing approaches to enquiry into perinatal death could be shared, and so that proposals for a possible standard approach could be discussed (Chalmers & McIlwaine 1980). Although draft proposals for a standard national enquiry process were drawn up, circulated for comment, amended and eventually published (Working Party on Confidential Enquiries into Perinatal Mortality 1980), it has proved difficult to achieve formal interprofessional agreement on these or any alternative proposals.

There are a number of likely reasons for the apparent lack of progress in achieving a national consensus on the form of a standard enquiry process. Firstly, by the late 1970s, many locally-based enquiries into perinatal death had been set up at area or regional level (Enkin & Chalmers 1980; Elbourne & Mutch 1981) and several of these subsequently become established on a continuing basis (Elbourne & Mutch 1984*a*). Understandably therefore, some local investigators have been reluctant to modify their existing enquiry design in the interests of national uniformity unless they can perceive clear dividends resulting from the effort which this would involve.

Secondly, many clinicians have been cautious about participating in any enquiry process which might involve judgments about the avoidability of indivdal perinatal deaths In part this reflects fear about possible legal repercussions: some obstetricians are concerned that the enquiry process may make litigation even more likely and promote defensive obstetric practice still further

(*Lancet* 1984), some paediatricians have expressed their concern that formal enquiry may increase the chances that they will be charged with murder in circumstances in which they and parents are already faced with harrowing decisions about the clinical management of particular babies These are not the only reasons why the attribution of 'avoidability' in individual deaths has been opposed, however: opposition has also come from those who have reservations about inferring causality by reference either to individual cases or uncontrolled case series (Dennis & Chalmers 1982, Tew 1982; Niswander *et al.* 1984). As Sir Dugald Baird said during discussion of this issue at the 1980 Study Group meeting, for example, 'I think it is a mistake to talk about avoidability of perinatal deaths. Who can tell whether a perinatal death could have been avoided? What one can do is to describe the circumstances in which the death occurred and the type of death and compare (these) with another area' (Baird 1980).

A third reason why progress towards a standard national process of enquiry into perinatal death has been slow relates to the sheer numbers of cases involved at national level (Godber 1976): there are still well over 5000 perinatal deaths in England and Wales every year, as compared with less than 500 maternal deaths in the year (1952) in which the national system of enquiry in maternal deaths was established in its current form.

Lastly, and in the spirit of the times, it has also been suggested (*Lancet* 1983) that the effort and cost involved in any ongoing enquiry process should be reflected in recognizable benefits.

One obvious benefit of these enquiries is the provision of good descriptive data describing perinatal outcome. The Scottish survey, for example, has generated important and frequently cited reference data on the causes and timing of perinatal deaths, and birthweight specific and gestational age specific mortality rates (McIlwaine *et al.* 1985). The surveys in Scotland and in the Northern and Wessex regions have all drawn attention to the refractory problem of antepartum intrauterine deaths among normally formed and relatively mature babies. These observations have emphasized the importance of assessing in well-controlled studies some of the many strategies used to screen for the compromised fetus during pregnancy; it is to be hoped, they will encourage clinicians and women to participate in the multicentre randomized trial of fetal movement counting which will be mounted later this year.

So far, it has to be said, there is no evidence that the ultimate purpose of enquiry into perinatal death—a reduction in the perinatal mortality rate—has been achieved more successfully in those areas in which enquiries have been mounted than in those in which enquiries have not been established (Elbourne & Mutch 1984*b*). There are several possible explanations for this finding, and it should not be used as an argument against mounting enquiries. But it is the kind of observation which gives weight to the recommendation of the Standing Joint Committee of the British Paediatric Association and the Royal College of Obstetricians and Gynaecologists that 'existing systems for the collection of perinatal mortality data should be used to the full before major new systems are launched nationally' (RCOG 1984).

What are the implications of these considerations? To begin with, because the variety of practical arrangements for ongoing enquiry into perinatal death which have evolved at local level reflect variations in local interest, resources and sensitivities, imposition of *complete* uniformity nationwide is undesirable, quite apart from being impossible. Nevertheless, *some* national standardization of the information collected and the way that it is presented is desirable both because (as Sir Dugald pointed out) interregional comparisons between the rates of different clinicopathological categories of death will be informative, and also because some of the rarer causes of perinatal death will demand a national approach to achieve a sample of sufficient size for meaningful investigation.

For both scientific and pragmatic reasons a standard, national process of ongoing formal enquiry into perinatal deaths should *not* be pursued with the objective of trying to decide whether individual deaths were 'avoidable', or indeed whether there were 'avoidable factors' associated with these perinatal casualties. Because of this, and because of the large numbers of perinatal deaths at national level, the model of the confidential enquiries into maternal deaths should be rejected as inappropriate for enquiry into perinatal death. Rather, formal enquiry into perinatal death should be based on analyses of carefully assembled numerator data (deaths) related to appropriately defined denominator data (all births). Using this epidemiological approach, the rates of clinically meaningful categories of perinatal death may be compared between and within regions, and appropriate further action taken when excess rates are observed.

The quality of the data required for an enquiry process based on these principles will continue to depend heavily on the quality and objectives of informal, hospital-based case reviews of individual perinatal deaths. Improvements in the quality of these reviews would make a dramatic difference to the quality of the national data which are already available for enquiry into perinatal death—those contained in the civil registration system (see paper by Alberman on p. 559). This publicly funded system will continue to exist whether or not the information collected within it is used for enquiry into perinatal death. Clinicians, civil servants and researchers therefore have a duty to ensure that they exploit the potential of the system as fully as possible.

The quality of most of the information collected at birth, stillbirth and death registration is good (Adelstein 1980). The system's main weakness relates to the information provided by clinicians. Greater efforts should be made, for example, to ensure that a birthweight is recorded for every baby. Final stillbirth and infant death certificates should only be completed by experienced clinicians (a consultant for all cases admitted to hospital), and then only after the histology is available and there has been time to review the sequence of events with staff (and perhaps the parents) (Working Party on Classification and Definitions 1980). Although an initial stillbirth or death certificate is often required for disposal of the body before all the information relevant for accurate completion is available, there are standard, but currently underexploited, procedures (Duley & Alberman 1984) through which entries on the initial certificates can be amended.

The anticipated introduction of the new stillbirth and infant death certificates (Gedella & Alderson 1984) at the beginning of 1986 provides an unprecedented opportunity for us to put our house in order and to exploit the civil registration system more fully for ongoing enquiry into perinatal death. Provided it receives basic data of good quality from clinicians, the Office of Population Censuses and Surveys will, from then on, be able to provide (at hospital, district, regional or national level) tabulations of perinatal deaths using one or more of the classification schemes which clinicians, pathologists and epidemiologists have found helpful for enquiry into perinatal death (Baird *et al.* 1954; Wigglesworth 1980; Clarke 1982). None of these developments will require significant extra resources; what they do require is enthusiasm and vision from those at national and local level who must make the necessary policy decisions and take action to ensure that the opportunity is not lost.

As Professor Alberman's paper in the current issue (p. 559) illustrates, data derived from the civil registration system can be used imaginatively for enquiry into perinatal death (Macfarlane & Mugford 1984). Although the level of detail in the data collected in the system is limited, the fact that it has been possible to overcome the problems of transferring birthweight from birth notifications to birth registrations has demonstrated that other valid information notified routinely to health authorities at the time of birth could also be transferred (after securing confidentiality). In future, therefore, if more detailed denominator data could be transferred, it might be possible to make the important distinction between those variations in death rates which reflect a fall in the incidence of predisposing conditions (placental abruption or idiopathic respiratory distress syndrome, for example) and those which result from differences in the case-fatality rates associated with these conditions.

For the time being, more detailed information for enquiry into perinatal death than that available through the civil registration system can be collected and analysed within the framework of health service information systems which refer to all registrable births, as in Scotland (Cole 1980). As reported in the January issue of the *Journal* (McIlwaine *et al.* 1985), a formal enquiry into perinatal deaths which began in Scotland as a research project (McIlwaine *et al.* 1984) has now been successfuilly incorporated into the framework of the routine health service information system (Information Services Division 1984). Within England, the Northern Region has so far come closest to establishing similar arrangements to those which now exist in Scotland Not only has a continuing, collaborative regional survey of perinatal mortality been established at little overt cost (Northern Regional Health Authority Co-ordinating Group 1984); the region has also developed a standard maternity information system for the collection of data on all births (Thomson &

Barron 1980). In future, as in Scotland, the Northern Region's perinatal mortality survey could either be incorporated within this health service information system or within the similar system which has been proposed by the Steering Group on Health Services Information (1984).

The Government has asked English Regional Health Authorities to implement health service information systems for maternity services by 1987 (Department of Health and Social Security 1984). Using the regional medical advisory machinery obstetricians and paediatricians can help to ensure that this opportunity to establish a more detailed basis for enquiry into perinatal death (and indeed, for perinatal surveillance more generally) is grasped effectively, as it has been in Scotland. As with the civil registration system, health service information systems will be established for 'administrative' purposes whether or not they are used for enquiry into perinatal death. It is up to 'non-administrators'—clinicians and others—to see that the potential of these systems is exploited as fully as possible for any purpose, including enquiry into perinatal death, which may help to improve the service. Certainly this means that clinicians should play their part by contributing valid data to these systems. But it also means that they should demand timely and meaningful information from those responsible for data processing at district, regional and national levels.

These developments in the civil registration and health service information systems provide an epidemiologically sound basis for answering calls for the establishment, through Britain, of an 'ongoing and formal process of enquiry' into perinatal death Apart from ensuring that these developments occur so that England, Wales, and Northern Ireland become as well served as Scotland is by its Information Services Division, are there other ways in which progress can be made? An important start could be made if those regions which have set up a formal process of enquiry into perinatal death (like Wessex, p. 550) could agree on some standard elements. Those involved in the Scottish and Northern Regional perinatal surveys, for example, are currently negotiating standard arrangements both for classifying perinatal deaths and for tabulating the data collected within their respective surveys. This collaborative initiative points to the means through which wider collaboration in enquiry into perinatal death can be achieved throughout the United Kingdom.

After consultation with those responsible for the enquiries into perinatal death in Scotland and the Northern Region, the Editorial Board of the *British Journal of Obstetrics and Gynaecology* has decided to publish a supplement on perinatal mortality in 1987, and triennially thereafter. In addition to relevant national data derived from sources already available, the first supplement will include data from Scotland and the Northern Region Any other region which wishes to consider submitting statistics for inclusion in the supplement is invited to write to the Editor to obtain details both of the basis on which deaths should be classified, and the form in which data should be presented. By encouraging inter-regional comparability in this way, it is hoped that the *Journal* can play its part in fostering the 'ongoing and nationwide process of enquiry into perinatal death' which has so far proved so elusive.

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Wessex Perinatal Mortality Survey 1982

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Summary. A survey of 335 perinatal deaths in the Wessex region revealed a perinatal mortality rate of 10·1 per 1000 total births. Lethal malformations accounted for 82 (24%) deaths. Of the 253 normally formed infants, 124 (49%) died during pregnancy and 33 (13%) in labour. More than 60% of the stillbirths weighed >1500 g. Of the 96 postpartum deaths, half occurred within 24 h of delivery, mostly following complications of labour and circumstances suggesting hypoxia. The Aberdeen classification showed half of the mothers had pregnancy complications: other predisposing factors were identified in 10% of perinatal deaths. There were 185 neonatal deaths of which 150 occurred within 7 days and 35 within the next 3 weeks. Sixteen (46%) of the late neonatal deaths were due to a congenital abnormality; pregnancy or labour complications were present in six (32%) of the remaining 19 normally formed infants. Review of existing methods of antenatal supervision in particular, followed by the use of better monitoring systems for earlier detection of fetal distress and prompt action when indicated, together with improvement in neonatal care in the first 24 h after birth should further reduce the perinatal mortality.

The object of the study reported here was to record all perinatal deaths of infants born in the Wessex region between 1 January and 31 December 1982; to identify factors associated with death; and to suggest how some improvement in the mortality rate might be achieved.

The population served by the maternity services is about 2¾ million with some 33 000 births per annum. In the 10 health districts there are 12 district hospitals providing consultant obstetric care and only one district has no neonatal intensive care unit. It is unusual for obstetric requirements to exceed local resources but limited paediatric facilities may necessitate transfer of infants to other units: infants may also be moved to specialized centres because of cardiac problems or for neonatal surgery. A thirteenth hospital provides consultant obstetric services for H.M. Forces. Seven of the district hospitals have attached but separately run general practitioner units and there are in addition 17 isolated general practitioner maternity hospitals in the region.

Materials and methods

The procedures described in the confidential paediatric enquiry into neonatal deaths in Wessex 1981 and 1982 (Wood *et al.* 1984) were followed. The midwives and paediatricians were asked to report all perinatal deaths as they occurred to the authors and to a central reference office. Family practitioner committees and coroners' offices also co-operated fully. Following notification, a prompt visit, often at a time to coincide with a perinatal meeting when the case was discussed, was made to the hospital con-

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cerned. The clinical and autopsy records were scrutinized and, where necessary, further information was sought from labour ward and nursery staff, general practitioners and community midwives. A proforma was completed and confidentiality ensured by using a code number. Examination of death certificate registers ensured no case had been missed. Postmortem examinations were carried out in 75% cases. Amongst those where no autopsy had been performed six infants were thought to have died from hypoxia.

The extended Aberdeen classification (McIlwaine *et al.* 1979) has been used but further information was obtained by means of the personal enquiry and sometimes a more precise cause of death was thus revealed.

Predisposing factors have also been identified as many of them may well have played as important a role as the various maternal conditions described in the Aberdeen classification. Because of the subjective judgment involved they have been described in some detail together with those cases where the patient herself may have contributed to the outcome.

As the circumstances surrounding early neonatal deaths are often very similar to those affecting the late neonatal group, details of the various factors which may have contributed to the death of all infants born in Wessex in 1982 and dying between the 2nd and 4th week have also been summarized as an addendum.

Small-for-dates has been defined as birthweight for gestational age below the 10th centile on the Aberdeen scale (Thomson *et al.* 1968).

Results

During 1982 there were 33 062 births in the Wessex region of which 86% took place in consultant units, 13% in the attached general practitioner units and maternity hospitals and 1% at home. There were 185 stillbirths and 150 first-week infant deaths giving a perinatal mortality rate of 10·1 per 1000 total births. Fifteen stillbirths and 18 postpartum deaths occurred in 25 multiple pregnancies and these 33 perinatal deaths accounted for 10% of the total and for 18% of the normally formed infants dying within 1 week. The small discrepancy in numbers reported in the OPCS Monitor (1983) which shows an additional 19 births (total of 33 081) and three fewer perinatal deaths (total of 331) may be due to the fact that this survey is concerned with infants born in Wessex and the civil registration with those whose mothers normally reside in this region.

The overall picture in Table 1 shows that 82 (24%) babies died from fetal abnormalities. Of the 253 who were normally formed, 124 (49%) died antepartum, 33 (13%) during labour and 96 (38%) after delivery. More than half of the babies had a birthweight >1500 g. Of the 96 born alive, 49 (51%) died within 24 h.

Fetal abnormalities

Fetal malformation accounted for 82 perinatal deaths and details of the abnormalities are shown in Table 2. Lesions involving the central nervous system, most with open neural-tube defects, accounted for a third, the majority

Table 1. Birthweights of all infants dying in the perinatal period by time of death in relation to labour*

	Birthweight (g)				
Time of death	≤1000	1001–1500	1501–2500	≥2501	Total
Antepartum	22 (5)	26 (1)	39 (3)	37 (0)	124 (9) 49%
Intrapartum	4 (2)	4 (0)	6 (1)	19 (1)	33 (4) 13%
Postpartum	39 (9)	21 (6)	11 (1)	25 (1)	96 (17) 38%
Total of normally formed infants	65 (16) 26%	51 (7) 20%	56 (5) 22%	81 (2) 32%	253 (30) 100%
Fetal abnormalities	3 (0)	13 (2)	32 (1)	34 (0)	82 (3)
Grand total	68 (16)	64 (9)	88 (6)	115 (2)	335 (33)

*Includes 33 perinatal deaths in 25 multiple pregnancies.
Number of deaths in multiple pregnancies shown in parentheses.

Table 2. Deaths due to fetal abnormality

Type of abnormality	Number of still-births	Number of deaths in first week	Total
Central nervous system	20	9	29
Congenital heart disease	1	13	14
Musculoskeletal system	1	11	12
Renal system	0	9	9
Multiple abnormalities	1	8	9
Chromosomal	1	3	4
Alimentary system	4	0	4
Hamartoma of lung	0	1	1
Total	28	54	82

Perinatal death rate from fetal abnormality = 2·5 per 1000 total births.

occurring in those units where serum α-fetoprotein investigations were not an established routine; 45% of the women were not screened, but the fact that two patients with normal serum levels subsequently gave birth to anencephalic fetuses shows the test is not infallible.

Normally formed infants

Table 3 gives details of the perinatal deaths of normally formed infants in different weight groups which have been divided into seven separate categories as in the Scottish Perinatal Mortality Survey (McIlwaine *et al.* 1979): it also shows the time of death in relation to labour. Antepartum haemorrhage and pre-eclampsia were the commonest complications, followed by mechanical problems in labour, maternal disease and haemolytic disease of the newborn. In 128 (51%) cases, none of these maternal complications occurred.

Antepartum haemorrhage (47 cases)

Placental abruption accounted for 35 cases which included 18 multiparae, two of whom had a previous history. Placenta praevia was recorded on five occasions, all infants being born alive. In the remaining seven, the cause of the bleeding was unknown. Of the 24 antepartum deaths, two died shortly after admission to hospital and the other 22 were dead on arrival. Fetal distress was noted in four of the eight deaths occurring in labour. Of the 15 postpartum deaths, antepartum haemorrhage alone was thought to be the main cause in seven, extreme low birthweight in two and birth hypoxia and respiratory distress were the major factors in the remainder.

Pre-eclampsia (41 cases)

Pre-eclampsia was defined in this study as a condition present in a patient whose blood pressure had risen to a minimum of 140/90 mmHg on more than one occasion after the 24th week when previously during the pregnancy it had been below this level. Sixteen (38%) cases occurred in multigravidae, six of whom had a previous history, and proteinuria was noted in a total of 15 (36%) cases.

There were 28 antepartum deaths, two occurred in labour and 11 after delivery. Sixteen infants were small-for-dates: in nine of them growth retardation in the fetus and in another four an unsatisfactory weight pattern in the mother (whose mean gain per week over a period exceeding a month before delivery was <0·25 kg) had been noted before any rise of blood pressure was recorded. The two intrapartum deaths occurring in mature infants were preceded by fetal distress. Of the 11 postpartum deaths, five developed fatal respiratory distress and another three failed to recover from the initial hypoxia. Although the remainder were born in good condition, two subsequently died from infection and the other succumbed to respiratory distress.

Maternal disease (15 cases)

Of the nine antepartum deaths, four occurred in women with essential hypertension and one with lupus erythematosus. Two more followed road traffic accidents. The remaining two were found in diabetic mothers, one of whom failed to comply with the strict treatment regimen required and the other developed severe pre-eclampsia. The intrapartum death of an infant of <1000 g was due to a retroplacental haemorrhage in a patient with essential hypertension. Two of the five early neonatal deaths were <751 g: in one, the mother suffered from essential hypertension and the other required an abdominal operation to remove an ovarian cyst. Another two succumbed to infection. One mature infant, whose mother had recently developed genital herpes, died from viral encephalitis and the other weigh-

Table 3. Categories of perinatal death at different times among all normally formed infants of various birthweights

						No maternal complications		
Time of death	APH	Pre-eclampsia	Maternal disease	Haemolytic disease	Mechanical	Low birth-weight	Normal birth-weight	Total
Birthweight ≤1000 g								
Antepartum	3	7 (2)	2	1	0	9 (3)	0	22 (5)
Intrapartum	0	0	1	0	1 (1)	2 (1)	0	4 (2)
Postpartum	5	2	2	0	1	29 (9)	0	39 (9)
Birthweight 1001–1500 g								
Antepartum	9	8	2	0	0	7 (1)	0	26 (1)
Intrapartum	1	0	0	0	2	1	0	4 (0)
Postpartum	7 (3)	3 (1)	1	0	0	10 (2)	0	21 (6)
Birthweight 1501–2500 g								
Antepartum	9	9	3	0	0	18 (3)	0	39 (3)
Intrapartum	3	0	0	0	0	3 (1)	0	6 (1)
Postpartum	2	2 (1)	1	0	2	4	0	11 (1)
Birthweight >2500 g								
Antepartum	3	4	2	2	0	0	26	37 (0)
Intrapartum	4	2	0	0	8	0	5 (1)	19 (1)
Postpartum	1	4	1	2	3 (1)	0	14	25 (1)
All weights								
Antepartum	24	28 (2)	9	3	0	34 (7)	26	124 (9)
Intrapartum	8	2	1	0	11 (1)	6 (2)	5 (1)	33 (4)
Postpartum	15 (3)	11 (2)	5	2	6 (1)	43 (11)	14	96 (17)
Grand total	47 (3) 18·5%	41 (4) 16%	15 6%	5 2%	17 (3) 7%	83 (19) 33%	45 (1) 18%	253 (30) 100%

Number of perinatal deaths in multiple pregnancies shown in parentheses.
APH, Antepartum haemorrhage

ing 1250 g, whose mother had been admitted with infective hepatitis, developed an apparently unrelated streptococcal septicaemia. The fifth small-for-dates infant of 1570 g, born to a hypertensive mother, required ventilation and later succumbed to repeated pneumothoraces.

Haemolytic disease (5 cases)

Three infants died before labour and two postpartum. One mother of three children, whose husband was rh-negative and who required a blood transfusion after her first delivery, was found to have rh antibodies at booking. Although the titre did not rise, the fetus died *in utero* at 39 weeks. In a second patient with one living child, routine testing showed no increase in anti-C antibody titre but the same sequence of events transpired. Autopsy confirmed the cause of death in both. Plasmapheresis failed to prevent the intrauterine death at 28 weeks of a third. In the case of both neonatal deaths plasmapheresis was carried out during the pregnancies and caesarean section performed at 33 and 36 weeks respectively, both mothers having become aware of reduced fetal movements. Both infants had immediate exchange transfusions but one of them lived only 2 h and the other, despite intensive treatment including peritoneal dialysis, died after 4 days.

Mechanical causes (17 cases)

Eleven infants were stillborn and six died after birth. Three stillbirths followed breech delivery: after an easy labour one, where there was also a possibility of Marfan's syndrome, was found at autopsy to have a tentorial tear, with another there was delay with the after-coming head and the third followed a difficult internal podalic version of a second very small twin. Two stillbirths resulted from shoulder dystocia, both infants weighing >4700 g, and prolapse of cord accounted for two more. Two infants were lost after vacuum extraction and forceps delivery respectively, both from tentorial tears. In an unattended delivery at home there was a precipitate labour with the infant falling to the floor and the last followed rupture of the uterus. Of the six postpartum deaths, four infants were delivered with forceps and all died from intracranial haemorrhage, one developed a large subdural haematoma following breech delivery and the other succumbed to birth asphyxia following vaginal delivery complicated by prolapse of cord.

Infants of low birthweight without maternal complications (83 cases)

Table 4 shows there were 40 stillbirths and 43 first-week deaths. Of the total, 53 (64%) were preterm, 21 (25%) were small-for-dates and the remaining nine (11%) not possible to classify because the fetus had been retained *in utero* after death for an uncertain time. A more detailed study reveals that 75% of the preterm infants were born alive but 86% of those which were small-for-dates were stillborn, findings remarkably similar to those reported in the Scottish Perinatal Mortality Survey carried out in 1977. Of the mothers bearing stillborn infants, six had a threatened abortion, three had noticed diminishing fetal movements for a week or more, three had an unexplained hydramnios, two had premature rupture of membranes with ensuing infection and four had an unsatisfactory weight pattern for a month or more before delivery (mean gain ≤0·13 kg/week). Only one infant was lost in each of the nine multiple pregnancies except in two instances. In one a prompt caesarean section for fetal distress failed to rescue either infant one of which was of normal birthweight: in the other the first failed to sursurvive a precipitate birth—its sibling, also extremely small, was stillborn after an internal podalic version and is listed in the 'mechanical' category. Twenty-one of the postpartum deaths weighed <751 g. Of the remaining 22, 12 had severe birth hypoxia, five developed respiratory distress despite good condition at birth and the other five died as a result of growth retardation, intra- or extra-uterine infection 'necrotizing enterocolitis.

Infants of normal birthweight without maternal complications (45 cases)

There were 31 stillbirths and 14 early neonatal deaths. In the former group, threatened abortion complicated one pregnancy, decreasing fetal movements for not less than 2 days were noted by three mothers and an unsatisfactory weight pattern (mean gain of ≤0·18 kg/week in varying periods of a month or more before delivery) was recorded in seven more. Death was preceded by fetal distress in two others. Of the postpartum deaths, five suffered severe birth hypoxia, one of which followed caesarean section for fetal distress, there were three 'cot deaths', two had infections, two followed rejection by their mothers after concealed pregnancies and labours and there were single cases each of congenital leukaemia and non-haemolytic hydrops.

Predisposing factors (26 cases)

After excluding 82 malformed infants and 38 weighing <751 g there remained 215 potentially viable infants and additional factors which may have contributed to the outcome were identified in 26 (12%) cases of which 15 weighed >2500 g and only five <1001 g.

In the antepartum group, there was a delayed response to warning signs discovered by fetal monitoring in three and the fourth patient failed to heed medical advice. There were 11 intrapartum deaths. Urgent delivery for fetal distress was advised for six mothers but there was a delay before the infant was born of >60 min where caesarean section was required and >30 min when forceps were used. In two others with fetal distress no treatment was undertaken at all: in one, there was a concomitant antepartum haemorrhage not seriously affecting the mother's general condition and in the other, where an unsatisfactory tracing was recorded, there was a communication failure between doctor and midwife. Another stillbirth followed delay in obtaining assistance with an instrumental delivery and there was an instance where a stillborn infant was delivered following uterine rupture after no advance for 12 h in strong labour and a history of previous caesarean section. The last of the cases in this group concerned an unattended birth, the mother having failed to send for any midwifery assistance.

Of the 11 postpartum cases, two patients con-

Table 4. Analysis of deaths in all normally formed infants of low birthweight

Time of death	Preterm	Small-for-dates	Gestation unknown	Total
Birthweight ≤1000 g				
Antepartum	1	5	3 (3)	9 (3)
Intrapartum	0	1	1 (1)	2 (1)
Postpartum	28 (9)	1	0	29 (9)
Birthweight 1001–1500 g				
Antepartum	1	3	3 (1)	7 (1)
Intrapartum	0	1	0	1
Postpartum	9 (2)	1	0	10 (2)
Birthweight 1501–2500 g				
Antepartum	10 (2)	7	1 (1)	18 (3)
Intrapartum	1	1	1 (1)	3 (1)
Postpartum	3	1	0	4
All weights				
Antepartum	12 (2)	15	7 (5)	34 (7)
Intrapartum	1	3	2 (2)	6 (2)
Postpartum	40 (11)	3	0	43 (11)
Total	53 (13)	21	9 (7)	83 (20)

Number of deaths in multiple pregnancies shown in parentheses.

cealed their pregnancies and labours and the infants died from neglect. Delayed treatment for fetal distress in circumstances similar to those with stillbirths occurred twice and a third followed the belated arrival of an anaesthetist whose 'bleep' had failed. Another infant thought to be of only 24 weeks gestation was unattended for 15 min until the weight of 810 g prompted urgent resuscitation but death ensued 3 days later. Infection was the cause of two other deaths. Endotracheal ulceration from a misplaced endotracheal tube leading to a tardily diagnosed candida infection accounted for one and the other resulted from a viral encephalitis following vaginal delivery by a mother suffering from genital herpes. Following premature discharge at 48 h of a 1000-g twin to another unit, there was delay in diagnosis of peritonitis which caused the infant's death in yet a third unit. The remaining two deaths occurred where infants were transferred from one unit to another because of lack of intensive care facilities or of the unit being overcommitted and were mainly administrative problems.

Additional data

After the exclusion of fetal abnormalities and twins (where gestational age may be difficult to judge) there remained 228 singleton perinatal deaths 57 of which were small-for-dates. Of the latter, no less than 50 (35%) occurred in 144 stillbirths. Most of these were discovered after delivery although some were recognized on admission to hospital often when the mother was in labour and the fetus dead. A few cases were diagnosed in the antenatal clinics but further investigation and treatment were pursued in only a minority.

Fetal distress in labour was recorded in 43 (17%) cases—15 intrapartum stillbirths and 28 neonatal deaths. The diagnosis had been made at each individual hospital but no precise definition was given.

Discussion

The fetal abnormality rate in Wessex in 1982 of 2·5 per 1000 births is considerably lower than that reported in Avon in 1976–1979 (Mutch *et al.* 1981), in Scotland 1977 (McIlwaine *et al.* 1979) and the Mersey Region 1979 (Mersey Region Working Party on Perinatal Mortality 1982) where rates between 4 and 5 per 1000 were recorded. Informed counselling made possible by increasing knowledge of genetics of those at risk of bearing malformed infants, improved diagnosis and routine screening programmes, facilities for therapeutic abortion and perhaps diet may all have contributed to bring this about together with the hereditary characteristics and environment of the population concerned.

About half (49%) of the normally formed infants died before the onset of labour and it is interesting to note that a similar figure (41%) was recorded in the Scottish survey. This finding must indicate some degree of failure in antenatal care. Organization, clinical methods, attitudes and modes of education have undergone little change for many years and need an entirely new appraisal. Other authors (Chng *et al.* 1980; Hall 1981) have emphasized these points and the Sighthill experiment (McKee 1982) demonstrated a new and apparently successful approach.

Although only 33 deaths were intrapartum, various predisposing factors were identified in a third and 76% of the total weighed >1500 g. Fetal distress preceded 43 (17%) perinatal deaths of normally formed infants suggesting the need for more efficient monitoring systems and better facilities for prompt treatment, especially as a third weighed >2500 g. Half of all post-partum deaths occurred in the first 24 h compared with 57% in the Avon study—facts again emphasizing the importance of management of labour and immediate post-delivery care of the infant. The introduction of formal labour ward rounds at stated intervals by senior staff might ensure improved teaching of all grades of staff, better management of patients and ensure more prompt intervention when indicated.

Only a few predisposing factors affecting the potentially viable infants were identified in the antepartum group where most deaths occur but

Table 5. Summary of data. Distribution of all perinatal deaths categorized according to extended Aberdeen classification

Classification	Stillbirths	First-week deaths	Total number	Death rate per 1000 total births
Fetal abnormalities	28	54	82	2·5
Antepartum haemorrhage				
Abruptio placentae	30	5	35	
Placenta praevia	0	5	5	
Other	2	5	7	
Total	32	15	47	1·4
Pre-eclampsia	30	11	41	1·2
Maternal disease				
Essential hypertension	5	2	7	
Diabetes	2	0	2	
Other	3	3	6	
Total	10	5	15	0·45
Haemolytic disease	3	2	5	0·15
Mechanical				
Instrumental	2	4	6	
Breech	3	1	4	
Prolapse of cord	2	1	3	
Other	4	0	4	
Total	11	6	17	0·5
Low birthweight (no maternal complications)				
Preterm	13	39	52	
Small-for-dates	18	4	22	
Gestation period unknown	9	0	9	
Total	40	43	83	2·5
Normal birthweight (no maternal complications)				
Normal	29	14	43	
Small-for-dates	2	0	2	
Total	31	14	45	1·4
Grand total	185	150	335	10·1

they were present in 33% of the intrapartum deaths and in 15% of those dying after delivery—a total of 26 cases of which 15 (58%) weighed >2500 g. There were occasions when these factors could not have been foreseen but, with a careful review of all circumstances surrounding each case and even within existing resources, it might be possible to anticipate similar episodes in the future. However, it must be said that the resulting overall impact on the perinatal mortality rate would be small—0·8 per 1000 in this series—and we must look elsewhere for any substantial improvement.

The Aberdeen system has been used to classify the perinatal deaths (Table 5) but it failed to reveal important data in a high proportion of postnatal cases (and rather fewer stillbirths) when, even if present, the underlying maternal condition appeared more as an incidental factor than a primary cause of death.

The high proportion of neonatal deaths in the first 24 h, also shown in the Avon study, reinforces the need for expert care during that vital time. However, many more infants are lost before the onset of labour so that any substantial reduction in the perinatal mortality rate will be achieved only by reducing the number of antepartum deaths. The need for more satisfactory methods to detect a compromised fetus mentioned in the Scottish survey is also clearly demonstrated here.

Addendum concerning the late neonatal deaths

By definition perinatal deaths are concerned only with stillbirths and infants dying within a week of delivery. With advance in knowledge

Table 6. Factors contributing to the death of normally formed infants aged between 8 and 28 days inclusive

Main infant complications (and birthweights)	Maternal complications			No maternal complications	Total number
	APH	Pre-eclampsia	Mechanical factors		
Respiratory factors (980 g—1 case) (2050 g—1 case)	Apgar <4, ventilated from birth	Apgar <4, ventilated from birth			2
Infection (1260 g—1 case) (1720 g—1 case) (>2500 g—5 cases)				Septicaemia 4 Pneumonia 2 Meningitis 1	7
Haemorrhage (850 g—1 case) (>2500 g—1 case)		Apgar <7, respiratory distress, intraventricular haemorrhage	Forceps delivery, ventilated after 24 h, intracranial haemorrhage		2
Haematological condition (2360 g—1 case)				Downs syndrome, leukaemia	1
Necrotizing enterocolitis (1570 g—1 case) (1320 g—1 case) (1170 g—1 case)	Apgar <7, attacks of apnoea	Apgar <7, respiratory distress syndrome		Apgar <7, respiratory distress syndrome	3
Sudden unexplained death (>2500 g—4 cases)				(4 cases)	4
Total (<2500 g— 9 cases) (>2500 g—10 cases)	2	3	1	13	19

Birth hypoxia assessed by 5-min Apgar score.

and the introduction of sophisticated methods of treatment many infants, who previously would have survived for only a short time, are enabled to live considerably longer and the circumstances surrounding their death may be similar to those dying in their first week. For this reason a brief summary of infant deaths occurring between the 8th and 28th day (inclusive) has been added.

Of the total 185 neonatal deaths recorded in Wessex during the year, 150 occurred in the first week—and have already been described—leaving 35 for further consideration. Sixteen (46%) had lethal malformations and details giving the causes of death of the remaining 19 normally formed infants, only four of which were not confirmed by autopsy, are summarised in Table 6. It also shows that underlying maternal conditions (as previously defined) were present in six (32%) cases and that these with other obstetric factors continued to play a significant role. Birth hypoxia was present in six infants and two of the cases of septicaemia involved infection with group B streptococci which were also isolated from the mother. It is also interesting to note that 14 (74%) weighed >1500 g at birth.

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Why are stillbirth and neonatal mortality rates continuing to fall?

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Summary. The Office of Population Censuses and Surveys are producing new annual tabulations including one on population birthweight distribution, and birthweight/cause-specific perinatal, neonatal and infant mortality rates. With these data it will be easier to distinguish between falls in mortality rates due to primary prevention of the causes, and those due to secondary prevention as a result of improved medical technology. Examples are given of the use of such data.

As in other parts of the developed world stillbirth and early neonatal mortality rates in England and Wales are falling rapidly and consistently, so that over the past 10 years the perinatal mortality rate has been decreasing at the rate of about 1 per 1000 births a year. Although there has been evidence for a shift to a later time of death for some infants, with a levelling out of postneonatal death rates, overall infant and childhood mortality rates are still falling so that there is a continuing improvement in survival.

It is as important to understand the reasons for falls in such rates, as for their increase. Improvements in the collection and presentation of national vital statistics now allow analyses which will help to distinguish effects of the primary prevention of the causes of such deaths from the secondary preventive measures which improved medical care can offer.

The following account is an attempt to demonstrate possible uses of recently available birthweight/cause-specific early mortality rates to begin to answer these questions.

Methods

Currently available statistics are fully described in the recent publication *Birth Counts* by Macfarlane & Mugford (1984).

The data to be described have been obtained from OPCS Monitors Series DH3 (81/4; 82/2; 83/1,2,3; 84/3,4,5,7; 85/1) and the annual reports on Mortality Statistics included in the Childhood and Maternity Series DH3 (1 to 11).

Problems arising in the use of these data are fully described in the relevant reports. Chief amongst them are the change from the use of the eighth revision of the International Coding of Causes of Disease (ICD) to the ninth revision in 1979. This affected both coding practices, and the grouping of birthweight which changed from being. ≤1000 g, 1001–1500 g etc, to: <1000 g, 1000–1499 g etc. The effects of such changes have been examined and described in a volume on bridge-coding between the eighth and ninth revision (OPCS—DH1 No. 10) and in Monitors (DH3 81/4 and DH3 83/3).

Individual birthweights for livebirths were first added to the available national statistics in 1975, when local health authorities were asked to make available to registrars of births and deaths the notified birthweight of each registered birth. The completeness with which this was done has increased from about 67% in 1978 to 96% in 1982 and virtually 100% later, but the data on which the present report is based are still largely estimated rather than complete. Moreover in some years, but not in others, there was a bias in that it was in neonatal deaths particularly that birthweight was most likely to be unknown These problems would not affect the principles upon which the present analyses are based, the validity of which will increase as data collection improves.

Statistics relating to incidence of a birthweight of ≤5½ lb (≤2500 g), by health authority, and mortality rates of such babies have been available since 1952 from DHSS return LHS 27/1. However, for all stillbirths, birthweight data have been collected and published since 1961 although the data have been incomplete and the grouping of birthweight variable.

Results

The most important indicator of high and low reproductive mortality risks is birthweight, so much so that even very small changes in distribution can affect the overall level of risk This holds true whether stillbirth or neonatal mortality risks are considered, although the relations between birthweight and stillbirth rate differ from those between birthweight and neonatal mortality rates.

Table 1 shows the estimated percentage distribution of birthweight in livebirths from 1979 to 1983. Even in these few years there have been some interesting trends, suggesting that there may be small increases occurring in both the lowest and highest weight groups, with a corresponding fall in the proportion weighing between 2500 and 3499 g. It seems unlikely that this pattern could be an artefact due to missing birthweight data, although the trends will need to be followed for future years before drawing any firm conclusions. When data for more years are available it will also be interesting to see to what extent demographic changes are related to this pattern, and whether it is in part caused by a shift from still- to live-births.

Birthweight-specific mortality 1979 to 1983

Table 2 shows estimated birthweight-specific mortality rates for stillbirths per 1000 total births, and for neonatal (first month) deaths per 1000 livebirths for 1979 to 1983. The high proportion with birthweight not stated in the stillbirths and neonatal deaths in 1981 and 1982 is notable, but for 1983 these proportions have fallen sharply. The consistently extremely high risk of low-birthweight births, particularly of neonatal death, but also of stillbirth is clearly shown, as is the slightly raised risk of the largest babies. Because of the varying proportions of 'not known' birthweight, trends over time should be treated with care, but the small increase over recent years previously shown in the proportion of livebirths below 1500 g seems to be well compensated for by the sharp fall in their mortality risk even over these few years. This interpretation is confirmed by the study of data produced directly from birth notifications by the Department of Health and Social Security (DHSS—LHS 27/1 for the years 1980 to 1983). The small increase in the proportion of liveborn babies weighing ≥4000 g was not accompanied by a fall in mortality rates until 1983.

In terms of impact on overall rates the most important changes are in the small group where the mortality is highest, for babies under 2000 g consistently account for more than half the stillbirths and neonatal deaths, and those weighing between 2000 and 2999 g for another quarter as is illustrated in Table 3. In this table the relative contribution made by each of the weight groups can be seen, since each rate is calculated out of

Table 1. Estimated percentage distribution of birthweight, livebirths occurring in England and Wales 1979–1983

Birthweight (g)	1979	1980	1981	1982	1983
<1000	0·72	0·20	0·23	0·24	0·27
1000–1499		0·52	0·55	0·56	0·57
1500–1999	1·2	1·3	1·2	1·3	1·3
2000–2499	4·5	4·8	4·5	4·6	4·6
2500–2999	19·6	19·2	19·0	18·8	18·6
3000–3499	39·2	39·1	39·0	38·7	38·7
3500–3999	26·9	26·9	27·2	27·3	27·4
≥4000	8·0	8·1	8·4	8·5	8·6
% livebirths with stated weight	67	87	96	96	99·9
Total livebirths (= 100%)	638 028	656 234	634 492	625 931	629 134

1979—estimates based on all available data, corrected for weight not stated. Source: OPCS Monitor DH3 82/2.
1980—estimates based on all available data, corrected for weight not stated. Source: OPCS Monitor DH3 81/4.
1981—estimates based on national 10% sample. Source: OPCS Monitor DH3 83/3.
1982 and 1983—estimates based on available full counts. Source: OPCS Monitor DH3 83/3 and DH3 84/5.

Table 2. Estimated birthweight-specific mortality rates per 1000, England and Wales 1979 to 1983

	Stillbirths*				Neonatal death†			
Birthweight (g)	1980	1981	1982	1983	1980	1981	1982	1983
<1500	238·0	209·2	181·2	173·5	395·8	312·7	293·0	295·5
1500–1999	88·8	80·8	70·1	69·0	74·5	55·2	49·5	46·6
2000–2499	23·2	21·2	19·8	19·2	17·7	14·8	12·6	13·3
2500–2999	5·2	4·8	4·9	4·9	4·9	4·1	3·5	3·7
3000–3499	1·9	1·8	2·0	1·7	2·4	1·9	2·0	1·7
3500–3999	1·4	1·3	1·2	1·3	1·8	1·6	1·3	1·4
⩾4000	2·2	2·4	2·1	1·7	2·3	2·1	1·5	1·5
Not stated	8·3	13·1	15·9	55·7	3·2	20·3	22·9	205·8
% birthweight not stated	15·2	9·1	11·2	1·4	5·8	14·0	16·1	4·9

* per 1000 total births: the denominator populations being as in the Monitors
† per 1000 livebirths: the denominator populations being as in the Monitors.
Sources: OPCS Monitors—DH3 82/4; 81/4; 83/2; DH3 83/1; DH3 84/3; DH3 84/5; DH3 84/7; DH3 85/1

Table 3. Perinatal and neonatal mortality rates distributed by birthweight group, England and Wales 1980 and 1983

	Perinatal mortality rate per 1000 total births of all weights		Neonatal mortality rate per 1000 livebirths of all weights	
Birthweight (g)	1980	1983	1980	1983
⩽1999	6·8	5·3	3·8	3·1
2000–2999	3·4	2·8	1·8	1 3
3000–3999	2·1	1·7	1·4	1·0
⩾4000	0·3	0·3	1·2	0·1
Not stated	0·7	0·3	0·4	0·3
All	13·3	10·4	7·6	5·8

Source: Tables OPCS Monitors DH3 83/1 and DH3 85/1.

total births of all weights, and this allows for the effect of changes both in proportion of risk group and birthweight-specific mortality. Such tables will become increasingly useful as the number of 'not known' birthweight cases falls.

Contribution of deaths with lethal malformations

In the past a serious constraint on the interpretation of birthweight-specific neonatal mortality has been an inability to distinguish between deaths caused by lethal malformation, where medical care can often only be palliative rather than curative, and those of normally formed infants.

For stillbirths it has been possible to go back some years, using a birthweight grouping fairly close to that in current use to look at trends in rates in those in whom cause of death was certified as being due to a congenital anomaly.

Table 4 shows stillbirth rates for the years 1975 to 1979 by birthweight, distinguishing between those certified as caused by a congenital anomaly and the remainder. These data suggest that as far as stillbirths are concerned the most marked falls in each weight group have been those due to congenital anomalies, although the stillbirth rates due to other causes have also fallen. Since we do not have complete birth ascertainment of all malformations, for most it is impossible to say to what extent the fall has been due to the primary prevention (or abortion) of affected fetuses, and to what extent medical care has kept alive affected births that would formerly have died. However, there has been a sharp fall in ascertained neural-tube defects of all weights (which are thought to be well reported) not entirely accounted for by abortion of affected fetuses (Table 5), suggesting that primary prevention, however effected, has played some part in this fall. But the decrease in perinatal deaths certified as due to congenital anomalies of the central nervous system has been even sharper than the fall in number of babies ascertained as having these anomalies.

Unfortunately we do not have reliable birthweight/cause-specific data for neonatal deaths until 1978, and it is not possible from published data to look at such trends until 1979 because of the change in the ICD grouping of birthweight. However, Table 6 gives such data as are available, based on estimated rates. Even allowing for the deaths without stated birthweight in 1981 and 1982 it appears that in the case of neonatal deaths the situation may be different, with much sharper falls in neonatal mortality in babies dying of causes other than congenital anomalies

Table 4. Stillbirth rates per 1000 total births certified as due to congenital anomalies (CM) and the remainder distributed by birthweight group, England and Wales 1975–1979

Birthweight (g)	1975	1976	1977	1978	1979*	% Fall 1975–1979*
≤2000						
CM	1·23	1·05	1·06	0·89	0·72	41·5
Other	3·09	2·93	2·93	2·63	2·57	16·8
2001–3000						
CM	0 40	0·39	0·38	0·33	0·30	25·0
Other	1·92	1·88	1·96	1·70	1·71	10·9
≥3001						
CM	0·24	0·19	0·19	0 14	0·14	41·7
Other	1·54	1·38	1·28	1 16	1·06	31·2
Not stated						
CM	0·46	0 48	0·35	0·37	0 29	37·0
Other	1·44	1·38	1·24	1·21	1·17	18·8
Total births	609 740	589 979	574 664	601 526	643 153	
Stillbirth rate	10·3	9·7	9·4	8·5	8·0	22·3

* Ninth revision birthweight grouping
Sources: OPCS Series DH3 1 to 1979.

Table 5. Number of babies with congenital anomalies reported to OPCS, those stillborn or first-week deaths, legal termination of pregnancy with central nervous system (CNS) anomalies, England and Wales 1974–1982

		Babies reported to have anomalies		Stillbirths and first week deaths and anomalies		Legal termination for CNS anomalies
Year	Total births	CNS	Other	CNS	Other	
1974	647 060	2 452	10 277	1 755	1 051	34
1975	609 740	2 227	10 003	1 576	962	73
1976	589 979	1 915	10 469	1 364	881	81
1977	574 664	1 896	10 533	1 279	845	124
1978	601 526	1 757	11 010	1 142	943	194
1979	643 153	1 637	11 892	1 006	1 035	285
1980	661 007	1 476	12 658	887	1 057	481
1981	638 699	1 229	12 221	636	954	441
1982	629 870	1 016	12 265	466	1 008	486

Sources: DH3 1-11, MB3 84/1, Weatherall (1982)

Table 6. Estimated neonatal mortality rates per 1000 livebirths certified as due to congenital anomalies and the remainder distributed by birthweight, England and Wales 1980 to 1983

Birthweight (g)	1980	1981	1982	1983	% Fall 1980–1983
≤1999					
CM	0·60	0·51	0·47	0·48	20·0
Other	3·24	2·47	2 36	2·60	19·8
2000–2999					
CM	0 92	0·73	0·65	0·72	21·7
Other	0·83	0·66	0·54	0·58	30·1
≥3000					
CM	0·74	0·61	0·60	0·55	25·7
Other	0·85	0·68	0·60	0·59	30·6
Not stated					
CM	0·10	0·25	0·31	0·07	30·0
Other	0·32	0·67	0·69	0·21	34·4
Total births	656 234	634 492	625 931	629 134	
Neonatal mortality rate	7·6	6·6	6·2	5·8	23·7

Source: OPCS Monitor DH3 82/2 and DH3 84/3

Discussion

These preliminary analyses of newly available birth data confirm the complexity of reasons for the continuing fall in stillbirth and neonatal mortality rates.

As far as distribution of birthweight is concerned the small changes which have occurred are tending to increase the births of the highest and lowest birthweight, the groups at highest risk, but also to increase the birthweight group at lowest risk, that of 3500 to 3999 g. For the low-birthweight groups the effect of the continuing sharp fall in birthweight-specific mortality rate outweighs by far the small increase in incidence, so that the absolute contribution to early deaths of this group is falling. Overall the preventive effect in respect to low birthweight seems to be due to secondary prevention, probably to improvements in medical care, rather than primary prevention. The shift towards higher birthweights at the other end of the spectrum may be the result of improved maternal health, possibly the result of primary preventive actions, but this needs to be related to demographic patterns before such a conclusion can be reached.

In contrast, there has been a marked fall in the contribution of stillbirths certified as due to congenital anomalies, and it can be seen from Table 5 that in part at least this is due to a fall in the number of births with neural-tube defects. Much, but not all of this fall is due to termination of affected pregnancies, but primary prevention of a nature we do not yet fully understand, must also be playing a role.

There has also been a fall, albeit on a smaller scale, of birthweight-specific stillbirth rates certified as due to causes other than congenital anomalies particularly in the weight group of ≥3001 g (Table 4), where the rate fell by 25% between 1975 and 1978, years in which the same birthweight grouping was used. This may well be the results of improved medical care, but again one would need to see whether there had been a demographic change, such as a reduction in first births, or of low social class which had contributed to the fall.

We do not yet have birthweight/cause-specific stillbirth rates for the years 1980 to 1983 but we do have such rates for the neonatal deaths where the reverse situation seems to apply Here it seems that the fall is more marked in the causes *not* certified as due to congenital abnormalities (Table 6), but we need to await the full data, stillbirth and neonatal deaths by birthweight and cause, before drawing definite conclusions.

In summary, these newly available data enable us to identify more closely the areas in which primary and secondary prevention are succeeding, and also those in which we seem to be failing to achieve any improvement. Analyses of this nature can supplement the type of data available from confidential enquiries and will make best use of our rapidly improving vital statistical system.

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Some characteristics of antenatal care in 13 European countries

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Summary. This study compares the organization of antenatal care in 13 European countries having a fetal and infant mortality rate below 20 per 1000. The countries differ in the number of prenatal visits, the role performed by midwives and the use of home care. It shows that there is no single model of antenatal care among countries having similar fetal and infant mortality.

A number of countries have shown a determination to assess the effectiveness of antenatal visits, screening procedures, and treatments provided during pregnancy (Enkin & Chalmers 1982) and international comparisons can usefully enhance that assessment. This study compares the conditions of routine prenatal care in 13 European countries which have similar fetal and infant mortality rates and whose health and socioeconomic level is comparable (Cochrane *et al* 1978).

Data

The Perinatal Study Group set up by WHO Regional Office for Europe carried out a survey in 1981 on how prenatal and perinatal care is organized in Europe. Data about obstetric intervention and definitions have already been published (Bergsjø *et al.* 1983; Mugford 1983) and a WHO report covering all the data is in preparation.

In this article the data concern countries having, in 1979, a fetal and infant mortality rate below 20 per thousand (WHO 1980): Belgium, Denmark, England and Wales, Finland, France, the Federal Republic of Germany (FRG), the German Democratic Republic (GDR), Luxembourg, the Netherlands, Norway, Scotland, Sweden and Switzerland.

Results

Number of prenatal visits

In general the state or the medical profession make recommendations about the number of visits for normal pregnancies and this varies from 3–4 to 14 (Table 1). Several countries have regulations defining the minimum number of

Table 1. Number of antenatal visits

	Legal or recommended number*	Average number actually achieved
Belgium	7†	ND
Denmark	10	8
Finland	14	14
France	7	5·9
Federal Republic of Germany	10	8·5
German Democratic Republic	10	ND
Luxembourg	5	5
Netherlands	12	12–14
Norway	14	‡
Sweden	12–13	14
Switzerland	3–4	5
UK: England and Wales	12–13	ND
UK: Scotland	12	10–12

* For uncomplicated pregnancies.
† French speaking community.
‡ 39% of the women have more than 10 visits.
ND No data.

visits necessary for a pregnant women to be eligible for prenatal allowances: four in France, five in Luxembourg, and eight in the FRG. In Switzerland the cost of only three visits is refunded by insurance if there are no medical complications.

The average number of visits actually made is not accurately known. Only Norway and France have recent national data; elsewhere the numbers derive from local surveys. But the available data do confirm the great variation in the recommended number of visits in each country; in particular Belgium, Switzerland, France and Luxembourg stand out in having a lower number of visits.

Role of obstetricians, midwives and general practitioners

Scandinavian countries and the Netherlands give an important role to midwives and, to a lesser degree, to general practitioners (Table 2). In Finland and Sweden, prenatal care takes place mainly in health centres and there midwives play a major role; they are responsible for approximately 10 of 13 or 14 visits planned. In the Netherlands, normal pregnancies are handled either by midwives (for 40% of the women) or by general practitioners (for 20% of the women), both in private practice and prenatal visits to an obstetrician are reimbursed only if there are medical complications. In Norway, care is essentially by general practitioners in health centres or in their own consulting rooms and by midwives in health centres. In Denmark, it is recommended that, at defined stages of the pregnancy, the women should go to a midwife centre (five visits), to a general practitioner's surgery (three visits), and to the antenatal clinic of an obstetric unit (two visits).

In the other countries obstetricians are more frequently responsible for prenatal visits, general practitioners less often, and midwives very infrequently. In Belgium, the FRG, Luxembourg and Switzerland, midwives rarely handle the visits; in France and in Great Britain, they more frequently carry out visits but rarely assume responsibility for the entire care of pregnancy. In the countries of this group, most of the midwives work in an antenatal clinic held in an obstetric unit and they most often assist the doctors during the visits. The obstetricians play an essential role in care in Belgium, Luxembourg, the FRG and the GDR. In France and in Great Britain they have an important role, but the care of pregnancies takes very varied forms: the women are sometimes seen regularly only by a general practitioner, more often only by the staff of a maternity unit; but the most frequent pattern is the 'shared care system' which combines several providers of medical care—generally the general practitioner and the maternity unit staff (Blondel 1985).

There are very few data about who is responsible for delivery in each country but it seems that antenatal and delivery care are often linked (Table 2). When midwives play an important role in antenatal care they are responsible for most of the normal deliveries. In Finland, Norway and Sweden, midwives attend all the normal deliveries; in the Netherlands if there is no medical complication, insurances do not cover specialist care during delivery and the women are attended by the same person (a midwife and to a lesser degree a GP) during pregnancy and delivery. In Switzerland and Luxembourg where specialists play a major role in antenatal care normal deliveries are supervised mainly by obstetricians. In France and above all in England and Wales midwives are more involved in care during delivery than during pregnancy.

Home visiting system

The provision of health workers to visit pregnant women at home does not seem to be linked to the other characteristics of antenatal care. The FRG, Luxembourg, the Netherlands, Norway and Switzerland have no home visits or provide them very exceptionally. Finland, France, the Netherlands and Sweden provide a planned home visiting system for particular cases such as women at high risk or non-attenders. In the other countries, Belgium, Denmark, the GDR and the UK every pregnant women should benefit from home visits but the application of this system varies in extent depending on area and in Belgium it is limited to women who go to a health centre.

Discussion

This study illustrates that there are wide national differences in the way prenatal care is conceived and delivered and there is no single model of prenatal care in a group of countries which have similar rates of fetal and infant mortality.

The description of prenatal care is limited in

Table 2. Persons in charge of care for uncomplicated pregnancies and deliveries

	Prenatal care				Delivery care			
	Qualification*				Qualification‡			
Country	Obstet Gynaecol.	Midwife	GP	Source†	Obstet Gynaecol.	Midwife	Other MD	Category of deliveries
Belgium	Yes	Exceptional	Yes	c	ND	ND	ND	
Denmark	2	5	3	ND	Yes	Yes	Yes	Normal only
Finland	No	10	3	r		100%		Normal only
France	Yes	Yes	Yes	c	41%	39%	20%	All deliveries
FRG	Yes	Exceptional	Yes	c	Yes	Yes	No	Normal only
GDR	ND	ND	ND	ND	Yes	Yes	No	Normal only
Luxembourg	4	Exceptional	1	r	Mainly	Yes	No	Normal only
Netherlands	No	Yes	Yes	r	40%	40%	20%	All deliveries
Norway	No	11	3	r		95%	5%	Normal only
Sweden	Yes	10	Yes	r		100%		Normal only
Switzerland	Yes	Exceptional	Yes	ND	75%	25%		Normal only
UK. Eng./Wales	Yes	Yes	Yes	c	10%	78%	12%	All deliveries
UK· Scotland	Yes	Yes	Yes	c	ND	ND	ND	

* Yes, exceptional, no or number of visits.

† Sources: r = recommendation or regulation; c = common practice

‡ Yes, no or distribution of deliveries according to qualification

ND No data.

the present study to a small number of characteristics. Moreover, the scarcity of national statistics and the lack of details about medical practice make it impossible to know with precision the importance of similarities and differences among the countries. In comparing prenatal examinations for example, a high number of visits may be a less important factor than the quality of these visits: care depends, indeed, very much on the type of examinations performed, and on the qualification and the clinical experience of the doctor or the midwife as well as on the degree to which the needs and the environment of the pregnant women are taken into consideration (Chalmers *et al.* 1980).

Prenatal care, as it is observed in each country, reflects the will of the state and of the medical profession to promote a given kind of prevention, but it is also determined by many factors. The resources of each country must play a part: financial resources, availability of qualified personnel and of equipment. Prenatal care cannot be isolated from the medical system and the social policy in each country and we have shown that it is linked to the organization of the obstetric care during delivery. Finally, prenatal care is largely influenced by the way in which maternity and prevention during pregnancy have been perceived over the course of time by the different social groups in each country (Oakley 1982).

The role of the specialist, the general practitioner, and the midwife is seen in a different way in each country and this survey and other publications have shown that in some countries the role of the midwife has tended to diminish over the last 40 years (Robinson *et al.* 1982; Phaff *et al.* 1975). As a result of their training and methods of practising, the obstetrician, the general practitioner and the midwife have a different approach to prenatal preventive care (Parboosingh & Kerr 1982; Zander *et al.* 1978). At a time when there is a great deal of discussion about primary care and when great importance is accorded to the needs of the pregnant women, to the continuity of care, and to health at the family level, it is illuminating to define the respective roles in European countries, of the obstetrician, the general practitioner, and the midwife.

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Unexplained infertility: a review

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Summary. When investigations fail to reveal a cause for infertility, treatment must then be based on possible, but unproven, causes, and since there is a high spontaneous pregnancy rate in unexplained infertility the effect of any treatment is difficult to assess. Such treatment has included correction of anatomical variants such as uterine retroversion and the use of hormonal manipulation during the follicular and luteal phases of the menstrual cycle. Ovum entrapment, occult spontaneous abortion and faults in sperm fertilizing capacity have all been implicated, and it is likely that immunological factors play a substantial role in unexplained infertility. Evidence does not support the use of bromocriptine in the absence of hyperprolactinaemia. Successful treatment by intrauterine insemination is unlikely if there are circulating anti-sperm antibodies in the partner. Improving cervical mucus by treatment with oestrogens and clearing infections with antibiotics may have a modest place but it is very difficult to show that these treatments have more than a placebo effect. Endometriosis is often missed and the possibility of it having developed after initial investigation warrants repeat laparoscopy after 2 years. Three approaches are currently acceptable in the management of the couple with unexplained infertility: await spontaneous pregnancy, the empirical use of clomiphene and in-vitro fertilization.

When conception fails to occur after a period of 1–2 years and no major or minor abnormality can be detected in either partner, then infertility is unexplained or 'idiopathic'. It is not possible to provide an actual incidence figure of unexplained infertility from the world literature due to variations in populations studied, selective referral of specific patient problems to individual specialists, the criteria used to determine normality and the interpretation of the semen analysis. An incidence of approximately 10% is probably reasonably accurate but the overall incidence is declining as couples are subjected to more complete and intensive investigation before being labelled 'normal but infertile'.

Criteria for unexplained infertility

Unexplained infertility should only be diagnosed when the woman has been shown to be ovulating regularly, to have patent fallopian tubes, no peri-tubal adhesions, fibroids or endometriosis and to have a sexual partner with normal sperm production. Intercourse must have taken place regularly, especially around the time of ovulation, and the infertility must be at least of 2 years' duration.

With increasing awareness in the population that many types of infertility are amenable to treatment, there is a tendency for couples with short-term infertility to seek medical intervention at an earlier stage than they would have done even 5 years ago. Before labelling a couple as infertile, and accepting that any pregnancy achieved subsequent to their presentation at the clinic is due to treatment, it is essential to acknowledge that couples with unexplained infertility of 1 year's duration have a high chance of a spontaneous pregnancy over the next 12 months. Wood *et al.* (1984) have reported pregnancy rates in normal couples with 1 year's infertility that show an interesting variation in the percentage who achieve pregnancy in the following 12 months related to the age of the woman at presentation. A 20-year-old woman with 1 year's infertility had a 76% chance of conceiving in the next 12 months. This chance of pregnancy decreased to 57% for a 30-year-old woman and was further reduced for a 40-year-old but remained at an acceptable level of 40% in these older women.

The reasons for the fall in the chance of a pregnancy with increasing age in a woman are not known but they may include a reduction in coital frequency (MacLeod & Gold 1953), the increasing occurrence of anovulatory cycles with increasing age (Brown *et al.* 1981), and abnormalities in the oocyte (Hertig 1975).

The investigations required to make a diagnosis of unexplained infertility include histological or biochemical confirmation of ovulation, hysterosalpingography, laparoscopy, a semen analysis and a postcoital test. The semen analysis is the least reproducible test between centres treating infertile couples and is also the most difficult to interpret. The values accepted for normality are arbitrary and in general indicate the artificial line between readily fertile and less readily fertile populations of men. We accept as normal a sperm density of ⩾20 million/ml but acknowledge that there are highly fertile individuals with sperm densities of <20 million/ml. Even within our accepted values of ⩾20 million sperm/ml the chances of pregnancy occurring within 12 months of presentation to a clinic are increased with an increase in sperm density. Wood *et al.* (1984) reported a 24% chance of pregnancy over a 12-month period in normal 30-year-old women with 3 years' infertility whose partner had a sperm density of 20 million/ml. In a similar group of women the chance of pregnancy over the following 12 months was increased to 34% if the partner had a sperm density of 100 million/ml.

Motility of the spermatoza is a most important aspect of the semen analysis. It is also frequently a highly subjective test and is usually overestimated as the observer's eye has a tendency to follow motile sperms and pay less attention to non-motile forms. Makler (1978) has reported an objective method for the determination of sperm motility. This is a multiple exposure photography method that allows one to determine the exact percentage of motility, individual and average speed, frequency of distribution of spermatozoal speed and spermatozoal concentration. Sperm motility assessed with this method is an average 20% lower than the value derived by subjective assessment. The widespread adoption of such a test would help in the comparison of potential male fertility in studies of unexplained infertility from different centres. We accept a subjectively assessed motility of ⩾40% with good forward progression as normal but acknowledge the inherent errors in such assessment.

The significance of spermatozoal morphology is unclear. McGowan *et al.* (1983) have shown a significant reduction in pregnancy rate with increasing levels of abnormal spermatozoa. While an increase in abnormal morphology may not be a serious barrier to conception, we do not include couples in our unexplained infertiliy group where >40% of the spermatozoa are abnormal.

While we exclude couples with an abnormal postcoital test result (PCT) from our 'unexplained' group, others do not or do not even perform this test because of doubts about its validity. As one of the reasons for a poor or negative PCT is sperm autoantibodies, a full semen analysis might usefully include a screening test for sperm antibodies in semen. The immunobead test (IBT) (Clarke & Baker 1982) is a reliable, valid test for seminal plasma IgG and IgA, it correlates well with mucus penetration *in vitro* (Baker *et al.* 1983) and in our laboratory is positive in 21% of the male partners in cases of otherwise unexplained infertility (Clarke & Baker 1982). Postcoital testing is only valid if done on the day of maximum mucus production. While pre-ovulatory mucus may be present for ⩾3 days, some infertile women may have only 1 day of rheologically normal mucus and the test must be done at this time if it is to have any significance. An abnormal PCT should be followed by in-vitro sperm–mucus capillary and contact tests. A normal PCT excludes a cervical factor but an abnormal PCT may indicate cervical mucus–sperm isoantibodies (Kremer & Jager 1976) or autoantibodies (Baker *et al.* 1983) particularly of the IgA class. Other causes of cervical hostility include cases where the mucus pH is <6·0 (Zavos & Cohen 1980) and a deficiency in cervical mucus sialic acid content (Lutjen *et al.* 1983).

Laparoscopy is essential in investigation of infertility, even when tubal patency has been demonstrated during hysterosalpingography, because extra-tubal adhesions and endometriosis can often only be diagnosed by this procedure. Drake *et al.* (1977) found that the addition of laparoscopy to their diagnostic screening tests reduced the number of patients who could still be said to have unexplained infertility from 10% to 3·5%, and El-Minawi *et al.* (1978) found pelvic pathology at laparoscopy in 57% of their unexplained group. The significance of minor pelvic abnormalities found at laparoscopy is, however, not entirely established. While it is appropriate to exclude women with minimal pelvic endometriosis or apparently minor tubal adhesions from the unexplained infertility group, it must be acknowledged that there are no long-term studies which define the adverse effects of these conditions on fertility in these women.

Treatment of unexplained infertility

The therapeutic approaches to unexplained infertility have ranged from simple reassurance to inspired empiricism. Anecdotal evidence is available that each form of therapy, conservative or aggressive, is associated with some success but the beneficial effects claimed for investigations (taking an active interest) or treatments (doing something positive) take little or no note of the possibility that the pregnancy might have occurred by chance. Kahn (1925), commenting on the beneficial effects of tubal insufflation reported by others, observed that he too had observed pregnancies following this procedure, the rate of which was inferior only to the pregnancy rate which he had noted following his taking blood for a Wasserman reaction! One of the more bizarre examples of the therapeutic effect of investigations is that reported by Hughes (1959) who found that the most fertile cycle observed in his patients was the one in which a luteal phase endometrial biopsy was performed. Any consideration of the effect of a therapeutic regimen must therefore take into account the natural history of unexplained infertility but studies that assess this factor are rare. Lenton *et al.* (1977*b*) investigated the eventual pregnancy rate in a group of patients with unexplained infertility who had been discharged from the hospital clinic since no further investigations or treatments were appropriate; they found that a couple with primary unexplained infertility had a 36·2% chance of conceiving over a 7-year period, whereas those who had previously achieved a pregnancy had a 78·8% chance of conception. Nonetheless, the fertility in this group was significantly lower than that in the population as a whole.

In our own clinic (McBain & Pepperell 1980), 35 couples with unexplained infertility of more than 2 years' duration (average 5·3 years) received seqential treatment with ethinyl oestradiol, clomiphene, bromocriptine and then artificial insemination with husband's sperm (AIH). Nine pregnancies occurred during treatment—four following treatment with clomiphene and five during treatment with bromocriptine. Sixteen of the remaining 26 patients (62%) conceived whilst on no treatment at all. Four conceived in the month immediately before starting treatment whilst basal hormone assays were being completed, three conceived during a break from treatment, five conceived in the 18 months after completing all the above treatments and the last four conceived between 18 months and 3 years after completing all therapy. By demonstrating such spontaneous pregnancy rates these studies have provided data for the assessment and treatment of couples with unexplained infertility. Pregnancies which follow empirical treatment, although gratifying, cannot necessarily be claimed as due to the treatment.

Most treatment regimens for couples with unexplained infertility have taken into account the possible causes (Table 1) and have made an attempt to treat them. Many of the initial approaches are now considered inappropriate although, for the purposes of completeness in this review, they will be considered.

Treatment of anatomical abnormalities

Operations for the correction of mobile uterine retroversion are seldom performed nowadays for unexplained infertility unless repeated postcoital tests show an absence of spermatozoa in the optimal mucus of a cervix which points acutely into the anterior vaginal fornix. An operation to correct this abnormality can only be justified if in-vitro sperm–cervical mucus testing shows normal sperm penetration. Equally, this problem could be overcome by intracervical AIH.

Although uteroplasty has been advocated for cases of unexplained infertility where a developmental uterine anomaly has been demonstrated (Carapetyan 1974), there is no evidence that

Table 1. Possible causes of unexplained infertility

1 Anatomical
    (a) Mobile retroversion
    (b) Uterine abnormality

2. Abnormalities of follicular development, ovulation and fertilization
    (a) Abnormalities of the oocyte
    (b) Hormonal abnormalities in the follicular phase
    (c) Ovum entrapment (luteinized unruptured follicle)
    (d) Abnormal fertilization
    (e) Hormonal or other abnormalities of the luteal phase

3. Immunological factors
    (a) Antibodies to spermatozoa

4 Cervical mucus abnormalities
    (a) Deficient production
    (b) Abnormal pH or constituents

5 Occult infections with mycoplasmas (cervical or seminal), ureaplasmas or chlamydiae

6. Occult endometriosis

7. Psychogenic and emotional factors

correction of a congenital uterine abnormality will improve the chances of conception. Uteroplasty is indicated, however, for the treatment of recurrent early pregnancy loss.

Treatment of abnormalities of follicular development, ovulation and fertilization

Oocyte abnormalities

Although Hertig (1975) has suggested that abnormalities of oocytes, ovulated during spontaneous ovulatory cycles, do occur, it is possible only to speculate on their incidence and importance as a cause of unexplained infertility. It is recognized that man is a rather subfertile mammal (Short 1979). According to Leridon (1977) such subfertility is, in terms of in-vivo fertilization, more apparent than real, 84% of all ovulated oocytes are fertilized in any particular month but only 36% of these conceptions survive to 6 weeks gestation and approximately 31% are born alive at term. Such unrecognized pregnancy wastage may be nature's ruthless way of discarding abnormal embryos (Short 1979). It has not been demonstrated so far, that unrecognized pregnancy wastage is more common in couples with unexplained infertility than in readily fertile couples. Using the model of clinical in-vitro fertilization (IVF), gross pregnancy rates are lower in unexplained infertility than in infertility due to tubal obstruction (Lopata *et al.* 1980; Trounson & Wood 1981), but there is no difference in pregnancy rates between these groups when embryo transfer is considered. That is, the lower pregnancy rate in couples with unexplained infertility taking part in an IVF programme is due to the more frequent failure of fertilization *in vitro*. Once that hurdle is cleared, the chance of pregnancy is not reduced in the unexplained infertility group.

Hormonal abnormalities in the follicular phase

In an intensive study of the follicular phase, we have observed that some patients with unexplained infertility had a low total urinary oestrogen excretion (<10th centile) during both follicular and luteal phases of the cycle and that treatment with clomiphene citrate increased the oestrogen levels to the upper part of the normal range. In nine such patients treated with clomiphene, only one conception occurred, a twin pregnancy resulting. Twenty-five patients with normal values for oestrogen and pregnanediol excretion in the follicular and luteal phase have also received treatment with clomiphene citrate but only three have conceived. In almost all these patients clomiphene therapy resulted in an approximate doubling of the pre-ovulatory oestrogen excretion, but the cervical score was significantly reduced from 6 days before, to the day of, the mid-cycle LH peak (McBain & Pepperell 1980). The reduction in cervical score is presumably due to the anti-oestrogenic effect of this agent even when administered in a dose of 25–50 mg/day for 5 days. Clomiphene is, however, the most frequently prescribed empirical treatment in couples with unexplained infertility and there is no doubt that both oestradiol and progesterone levels are 'improved' (or at least increased). Although there are no controlled studies available to compare the cumulative pregnancy rates achieved with clomiphene and placebo in regularly ovulating women, its continued widespread use suggests that it is conventional wisdom that clomiphene treatment encourages conception or at least does not hinder it.

Gonadotrophin therapy has also been used to 'improve' follicular development (Sher & Katz 1976). As no large series showing the effect of gonadotrophin therapy in unexplained infertility has been published there is no good evidence for an enhanced pregnancy rate from such treatment; the cost, the need for close biochemical and ultrasonic follicular monitoring and increased risk of high multiple pregnancy are sufficient reasons to limit its use at present. This apart, Fleming *et al.* (1982) reported a more promising use of gonadotrophins. Their earlier work (Dodson *et al.* 1975) had suggested that some women with unexplained infertility had inappropriately early LH surges an evidenced by the detection of an LH surge in response to lower levels of plasma oestradiol than is usually seen at mid-cycle in fertile subjects. Fleming *et al.* (1982) treated five such women with an LH-RH analogue to induce a hypogonadotrophic state which was then treated with gonadotrophins, some pregnancies resulted but it is difficult to know how far these can be attributed to the treatment.

Apart from increasing hormone levels and possibly improving the quality of ovulation (a most imprecise quantity), ovulation-induction agents may have another place in the treatment of women with unexplained infertility. McBain *et al.* (1980) showed that clomiphene citrate and gonadotrophins, or these agents used in combination, significantly increased the number of follicles available for aspiration in regularly ovulating women undergoing IVF. If the chance of pregnancy is limited each month by the ovulation of only one oocyte then perhaps the chances will be improved if multiple follicular development and ovulation is induced.

Ovum entrapment

The luteinized unruptured follicle syndrome was first described by Jewelewicz (1975). In this condition there is presumptive evidence of ovulation (i.e. biphasic basal body temperature, secretory endometrium, and increased progesterone or pregnanediol levels) but there is no stigma on the corpus haemorrhagicum or the corpus haemorrhagicum is absent. This concept was investigated by Marik & Hulka (1978) who laparoscoped their patients in the first few days after ovulation to observe the corpus haemorrhagicum. Their criterion of ovulation was the presence of a recognizable stigma where the oocyte had been released from the follicle. They found that 31% of patients had luteinized unruptured follicles by this definition. The significance of this observation as a possible cause of unexplained infertility was diluted by the fact that 'unruptured follicles' were frequently observed in patients with significant pelvic and tubal pathology as well as in these with unexplained infertility. Moreover, conception occurred subsequently in untreated patients as well as in clomiphene-treated patients in whom this tentative diagnosis had been made. The role of the leutinized unruptured follicle in unexplained infertility is unknown and, even where it has been found to occur, the place of treatment, except IVF, is unclear.

Fertilization abnormalities

There is some evidence that fertile women trying to conceive have a high incidence of occult abortion. Apart from the studies of Hertig (1975) and the calculations of Leridon (1977), a high rate of early pregnancy wastage has been demonstrated in fertile women by the detection of β-hCG and early pregnancy factor (EPF). Edmonds *et al.* (1982) claimed that 60% of cycles were conceptual in such women on the basis of elevated β-hCG levels in the late luteal phase and found that 60% of these β-hCG positive conceptions were early pregnancy losses. This observation has not been supported by another group (H.W.G. Baker, 1984, personal communication) and is not a frequent finding in women with unexplained infertility (McBain & Pepperell 1982). It may be, however, that a more appropriate test might be the measurement of EPF in these women. There are two further studies in the literature which demonstrate pregnancy levels of this factor in the luteal phase of women trying to conceive but whose menses are not delayed, or delayed by only a few days. Rolfe (1982) found EPF in 18 of 28 cycles only four of which continued as recognized pregnancies. Similarly, Smart *et al.* (1982) investigating 21 previously fertile women trying to conceive found EPF in the sera of 14, six of these 14 women showed only a transient rise in EPF and it is interesting that none of these six had pregnancy levels of β-hCG. It is possible that the difference in incidence of occult abortion in terms of β-hCG may be explained by differences in specificity of the β-hCG assays but further investigation of EPF levels in women with unexplained infertility are needed before any further comment can be made.

In an attempt to assess the fertilizing capability of oocytes in patients with unexplained infertility the two IVF teams in Melbourne have attempted in-vitro fertilization procedures in such patients. It had been hoped that some of these patients would conceive and that others, whose ova could not be fertilized, could be detected and advised that further assessment and treatment was inappropriate as a pregnancy was most unlikely. Although some women did fall into the group where none of the ova obtained could be fertilized, many of these women have since conceived spontaneously. Many others have conceived during an IVF treatment cycle and still more have conceived spontaneously while having a break from IVF treatment but where previous treatment cycles have resulted in embryo transfer but no pregnancy.

Luteal phase abnormalities

In contrast to the follicular phase of the cycle, the unequivocally fertile luteal phase cannot be studied in its entirety as the hormone secretion from the implanted blastocyst prevents involution of the corpus luteum. In the present state of our understanding, adequacy of the corpus luteum is a function of its ability to secrete sufficient progesterone for an adequate period of time to allow implantation to occur in a well-formed secretory endometrium. After implantation the corpus luteum must be capable of responding to rising levels of hCG from the blastocyst by continuing to secrete amounts of progesterone which are adequate to induce a stable decidual reaction in the endometrium.

Abnormalities of luteal phase function may involve the whole luteal phase or may be confined to the 5–7 days following ovulation. The latter abnormality is often suggested by the observation of a slow rise in basal body temperature after the time of presumed ovulation, but when one remembers the unsatisfactory correlation between basal body temperature recording and plasma progesterone levels (Johansson *et al.* 1972), this observation is only tenable if mid-luteal phase levels of progesterone or pregnanediol are within the ovulatory range. If not, one has observed an anovulatory cycle. In a detailed study, Sobowale *et al.* (1978) measured the daily plasma levels of FSH, LH, oestradiol and progesterone in 23 cycles in 18 normal women, eight of whom were trying to conceive. These authors noted a significant reduction in plasma progesterone levels from day 3 to day 7 of the luteal phase in patients who were trying to conceive but failed to do so, compared with the levels observed in the five patients who did conceive and the 10 who were not exposed to pregnancy. However, one of the 'low progesterone secretors' conceived shortly after the study period.

Overall inadequacy of the luteal phase may be diagnosed histologically or by hormonal criteria. Noyes (1956) proposed that the diagnosis should be made when endometrial development lagged at least 2 days behind that expected according to the dates of ovulation and onset of menses. He also recommended that the endometrial biopsy should be taken from the uterine fundus as the response of the endometrium of the lower uterine segment to progesterone was not uniform. Hormonal assessment has now largely replaced the biopsy assessment of this abnormality, however, blood or urine specimens for measurement of progesterone or pregnanediol levels respectively should be collected on at least three occasions between 11 and 4 days before the next menses (Abraham *et al.* 1974).

The cause of *luteal phase inadequacy* still remains obscure, although there is no doubt it may follow poor follicular development. The role, if any, played by oestradiol and prolactin in the luteal phase of the spontaneous cycle is undetermined, although there is some evidence that high levels of both hormones may be luteolytic (Stouffer *et al.* 1977).

The dopamine agonist, bromocriptine, has been shown to be effective in treating the inadequate luteal phase when hyperprolactinaemia is the cause of the ovulatory disorder (Del Pozo *et al.* 1979). Lowering the serum prolactin level leads to an increase in progesterone secretion, a restoration of luteal phase length to normal and pregnancy may occur. Muhlenstedt *et al.* (1978) reported four pregnancies in seven hyperprolactinaemic women, who had a short luteal phase, after bromocriptine therapy, and two pregnancies in 11 normoprolactinaemic patients with a short luteal phase who also received bromocriptine. Bromocriptine has also been used to treat unexplained infertility in women in whom serum prolactin levels were not elevated and luteal function was apparently normal. Lenton *et al.* (1977*a*) treated a group of 40 patients with unexplained infertility with bromocriptine alone, or bromocriptine plus clomiphene for up to 9 months; 13 patients (33%) conceived during treatment.

Two double-blind trials of bromocriptine and placebo have since shown that this drug is of no value in patients with unexplained infertility. Wright *et al.* (1979) found that 29% of 24 patients treated with bromocriptine for a 6-month period conceived, but so did 22% of the 23 patients who received placebo. In a crossover double-blind trial of bromocriptine plus placebo (3 months treatment with each agent) McBain & Pepperell (1982) reported 18 pregnancies in 50 patients with unexplained infertility: five occurred during the observation cycle before treatment, four occurred during treatment with placebo, four during treatment with bromocriptine and five during a subsequent follow-up period of 12 months.

Clomiphene citrate, given to improve the follicular phase and thus also the luteal phase, and progesterone suppositories have also been used to treat luteal phase inadequacy, but definite proof of their effectiveness is not available.

Treatment of immunological factors

Antibodies to spermatozoa

Where anti-spermatozoal immobilizing antibodies are present in the sera of either partner the postcoital test or semen analysis or both are usually abnormal and the patient is not labelled as having 'unexplained infertility'. The effect and role of agglutinating antibodies in sera is much less clear, however. Sperm-agglutinating antibodies of the IgA class in cervical mucus are a cause of infertility and where a cervical factor is demonstrated by in-vitro sperm–mucus cross-testing, such antibodies should be sought. Clarke *et al.* (1984) using the IgA immunobead test detected significant levels of IgA in the mucus of 13 of 70 women with unexplained infertility.

In an attempt to overcome any local effect of anti-sperm antibodies in the cervical mucus, patients were treated with intrauterine AIH by instilling 0·5 ml of fresh semen directly into the uterus through a small polythene catheter. The only beneficial effects occurred in patients with cervical mucus immobilizing antibodies, but no circulating immobilizing antibodies, almost 40% of such patients conceived.

The use of AIH in patients with completely normal postcoital tests, and thus unexplained infertility, has been a dismal failure.

Antibodies to zona pellucida

A small number of patients with unexplained infertility were thought to have autoantibodies to the zona pellucida of their oocytes (Shivers & Dunbar 1977; Lopata *et al.* 1980). The original tests used were subject to non-specific interference and after these antibody-positive women were tested with the specific assay (Nayudu *et al.* 1981) it was shown that zona antibodies were not present in the follicular fluid or sera of infertile women. Antibodies to zona pellucida are now discounted as a cause of unexplained infertility (Wood *et al.* 1984).

Treatment of cervical mucus abnormalities

The mucus secretion from the endocervix undergoes marked variations during the ovulatory cycle and patients may recognize these changes subjectively (Billings *et al.* 1972). Daily cervical mucus assessment by the clinician shows dynamic changes in mucus volume, spinnbarkeit and ferning of the dried preparation. A simple scoring method for each of these factors, in addition to changes in the diameter of the external os, allows the total cervical score to be calculated (Insler *et al.* 1972). Moghissi *et al.* (1972) exclude cervical diameter from their cervical score assessment, but include the viscosity and cellularity of the mucus.

In the individual patient, the cervical score increases in parallel with the pre-ovulatory rise in oestrogen excretion, but marked individual variations in cervical score are apparent in patients with similar peak urinary oestrogen excretion. Our data on serial cervical mucus scoring relative to the pre-ovulatory LH peak show that no correlation exists between peak urinary oestrogen excretion and total cervical score (McBain 1980). Despite the uncertain relation between oestrogen levels and the cervical score, and the variability in cervical score after pharmacological doses of oestrogen, supplementary oestrogens have commonly been prescribed for patients with suboptimal cervical mucus production.

A definite correlation does exist between the timing of mucus collection and the result obtained during the postcoital test, as cervical mucus is most receptive to spermatozoa on the day before and the day of the pre-ovulatory LH peak (Kerin *et al.* 1976); it is essential to identify this mid-cycle marker before one can assess the adequacy of the cervical means.

It is established that exogenous oestrogens, when given in sufficient dosage to amenorrhoeic or postmenopausal women, will stimulate the secretion of cervical mucus with properties identical to those observed in the pre-ovulatory period of the spontaneous cycle (da Paz 1951). It has not been shown, however, that oestrogens given in doses insufficient to inhibit ovulation have any beneficial effect on the properties of pre-ovulatory cervical mucus. More importantly, even in the absence of a beneficial effect upon its target organ, such therapy has not been shown to be associated with an improvement in fertility and treatment with 10 μg/day of ethinyl oestradiol has been associated with anovulation in 10% of previously ovulating patients (McBain & Pepperell 1980).

Apart from treatment with oestrogen, antibiotics have also been used in an attempt to 'improve' cervical mucus. The rationale for such therapy has been the treatment of chronic cervicitis. The diagnosis of chronic cervicitis tends to be maintained despite repeatedly negative bacteriological findings, unlike the situation pertaining to suspected infections in other parts of the body. The view that antibiotic therapy has no place in the treatment of poor sperm–cervical mucus interaction is perhaps over-simplistic since Insler *et al.* (1977) found that sperm penetration of cervical mucus improved in six of eight couples treated with doxycycline for 7 days, despite negative bacteriological findings. They did not apparently attempt to culture anaerobic organisms, *U. urealyticum* or chlamydia so that their reported findings, although helping to clarify the situation, are incomplete. Additional studies are needed before chronic cervicitis can be dismissed as a possible cause of unexplained infertility.

Treatment of occult infections with mycoplasmas, ureaplasmas or chlamydiae

Gnarpe & Friberg (1973) reported a 27% conception rate in patients with unexplained infertility in whom a proven infection with T-strain mycoplasma (*U. urealyticum*) had been treated with doxycycline for up to 5 months. The minimum period of infertility in their series was 5 years. Doxycycline was given to both husband and wife for 10 days from day 7 to day 16 of each treatment cycle. Although the mechanism by which subclinical infection with *U. urealyticum* may cause unexplained infertility is uncertain, Friberg (1978) quoting Gnarpe claimed that some strain of *U. urealyticum* isolated from infertile couples have been shown to produce a neuraminidase-like substance and suggested that the oocyte may be fertilized by a sperm that is colonized by *U. urealyticum*. The infected zygote may then fail to grow for one or two reasons; either a lethal chromosomal aberration may occur or neuraminidase-like activity may prevent implantation, as has been reported in the mouse (Porter 1975). By contrast, De Louvois *et al.* (1974) have demonstrated significant numbers of *U. urealyticum* in the semen and cervical mucus of fertile subjects and they have raised doubts about the significance of these organisms as a cause of infertility. Friberg (1978), however, suggests that only certain strains of *U. urealyticum* may cause infertility. There is no doubt that a 27% conception rate within 5 months in unexplained infertility is impressive. When a definite cause of infertility is identified and is completely treated, as was presumably the case in the series reported by Gnarpe & Friberg (1973), one could reasonably expect a pregnancy rate greater than 27% over a 5-month period in patients who were normal in every other respect. As the conception rate was less than would be expected after 5 months in an unselected general population, the possibility remains that the treatment played no useful role other than that of placebo.

Although *Chlamydia trachomatis* has been clearly associated with acute salpingitis, it is unclear whether subclinical or asymptomatic tubal or peritoneal infection occurs and whether unexplained infertility may result. As this organism is also sensitive to treatment with doxycycline, such antibiotic therapy may be effective in eradicating any chlamydial infection and this has been the basis of previous therapy.

Occult endometriosis

Moghissi & Wallach (1983) in a review article on unexplained infertility pointed out that any one factor, considered to be within normal limits and compatible with fertility at the onset of the investigation, may have changed with an increasing duration of infertility. It is the practice in our clinic to repeat tests of ovulation and semen analyses at regular intervals in couples who remain infertile. We also perform a repeat diagnostic laparoscopy if 2 years have elapsed since the initial normal laparoscopic findings and have discovered endometriosis in approximately 20% of these previously normal subjects. This would suggest either that endometriosis was present at the initial laparoscopy but was missed, which we naturally believe to be unlikely, or that it has developed in the 2-year interval. In such cases, the thesis might be advanced that as these women were infertile before endometriosis was detected, the endometriosis now present may be associated with their infertility rather than being the cause of it. Brosens *et al.* (1978) observed the phenomenon of luteinized unruptured follicles significantly more often in women with endometriosis than in those in whom there was no sign of endometriosis. The same workers (Koninckx *et al.* 1980) subsequently showed that women with luteinized unruptured follicles had significantly lower mean levels of progesterone in posterior cul-de-sac fluid than those in whom an obvious ovulatory stigma was observed. While they found cells of endometrial origin in the posterior cul-de-sac in women in both groups, they believed that this was the result of microscopic retrograde menstruation which is inevitable in the presence of patent fallopian tubes. Women with high local levels of progesterone did not develop endometriosis because these high progesterone levels inhibited endometrial cell implantation and growth, but in women with luteinized unruptured follicles who have low local progesterone levels endometriosis can develop. So that, at least in the initial stages, endometriosis is a sign rather than a cause of infertility, and failure of the oocyte to extrude is the reason for the infertility.

With IVF the follicle is punctured and the oocyte is aspirated. If the enclosed oocyte does not differ from those which are ovulated spontaneously and if the defect lies only in the extrusion of the oocyte, then IVF is a logical treatment of the luteinized unruptured follicle syndrome and, by inference, endometriosis.

Psychogenic and emotional factors

It is often very difficult to separate emotional and psychogenic factors which occur during treatment for infertility, especially where a treatment programme is intensive or prolonged, from those which might have been present initially and played a role in the continuing infertility. Couples with normal sexual function before the infertility may develop decreased coital frequency, orgasmic dysfunction, mid-cycle male impotence, and even anovulation. Suicide is also twice as common in childless couples than in those with children.

No controlled trial of psychotherapy in patients with unexplained infertility has yet been reported to be better than placebo, however, there is little doubt that the patient's confidence in the consultant who takes time to assess the problem and gives detailed explanations concerning diagnosis and treatment regimens is probably as important as the various treatments. The fact that expensive medications seem to work 'best' may be consistent with the feeling that some patients obviously have i.e. 'if it's *that* expensive, it must be good'.

Even the psychological support given by a drug-induced or spontaneous pregnancy may be sufficient to overcome any anti-fertility psychogenic or emotional factor. In our own study, four patients who conceived on 'active' therapy for their first pregnancy have since conceived again. One required clomiphene citrate on both occasions but of the remaining three, who required bromocriptine initially, two conceived spontaneously the second time and one required bromocriptine again. Three patients who conceived spontaneously for their first pregnancy, repeated this performance.

What is a rational approach in 1985?

After complete investigation the patient should be reassured that 'everything is normal' and that the probability of a spontaneous pregnancy during the next 12 months to 2 years is high. Only where the patient is emphatic that some treatment is necessary, should a therapeutic programme be devised. Clomiphene citrate is still the most commonly used agent under such circumstances, the rationale usually being the increased chance of success because of the increased incidence of multiple ovulation. Whether the increased oestrogen levels following treatment outweigh the anti-fertility effect on the cervical mucus is not known. There would appear to be little basis for continuing this therapy for more than 3–4 months.

Treatment with bromocriptine is inappropriate unless the serum prolactin levels are elevated, intrauterine AIH is of no value when the postcoital test is normal, and the place of antibiotic therapy to eradicate occult infections or improve cervical mucus is unclear.

Now that IVF is available in most countries of the world, this treatment should be made available to couples with unexplained infertility but probably not until at least 2 years after the completion of investigations and empirical therapy. When the success rate of IVF increases above 20% per cycle, the current success rate in Melbourne, a reduction in this time limit might be considered. Currently the chance of spontaneous conception is higher than that within an IVF programme for most couples with unexplained infertility, unless their infertility is of long duration.

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Immunoreactive prostacyclin and thromboxane metabolites in normal pregnancy and the puerperium

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Summary. Prostacyclin and thromboxane have been implicated in the pathophysiology of several disorders of pregnancy, but there is little information on concentrations of these prostaglandins in normal pregnancy. The aim of our study was to determine the range of values throughout normal pregnancy and the puerperium and to compare this with concentrations in normal non-pregnant women. Measurement was by radioimmunoassay of prostacyclin and thromboxane metabolites. We observed a significant difference in prostacyclin metabolites in the first trimester, (mean 19·9, SEM 0·96 pg/ml) compared with the normal non-pregnant group (mean 15·9, SEM 0·68 pg/ml). There were no significant differences between values in the normal non-pregnant group and those in the second and third trimester or postnatally. The increase in prostacyclin in the first trimester may be associated with placentation and physiological vasodilation, and insensitivity to angiotensin II seen in early pregnancy. We noted a significant reduction in thromboxane metabolites in the second (mean 133, SEM 14·9 pg/ml) and third (mean 123, SEM 10·7 pg/ml) trimesters and the puerperium (mean 119, SEM 6·3 pg/ml) compared with the values in the normal non-pregnant group (mean 142, SEM 4·9 pg/ml). This may be due to increased platelet stability or decreased thromboxane synthesis.

Prostaglandins have long been known to have physiological roles in pregnancy and parturition. Prostacyclin (PGI_2) and thromboxane (TxA_2), which are powerful vasoactive agents, can now be readily assayed, and there is increasing evidence implicating them in the pathophysiology of several disorders of pregnancy. In pregnancy-induced hypertension (PIH), several workers have shown a reduction in PGI_2 production from fetal (Remuzzi *et al.* 1980; Downing *et al.* 1980) and maternal (Bussolino *et al.* 1980) vascular tissue, and low prostacyclin-like activity in amniotic fluid (Bodenta *et al.* 1980). In intra-uterine growth retardation (IUGR) PGI_2 production has also been shown to be low (Stuart *et al.* 1981; Jogee *et al.* 1983).

Many of the changes seen in PIH and IUGR, such as platelet consumption, vasoconstriction and low renin secretion may result from PGI_2 deficiency, as PGI_2 is a potent vasodilator. platelet inhibitor and renin secretion stimulant (Miyamori *et al.* 1979). More recently, PGI_2 has been shown to be directly related to umbilical blood flow (Makila *et al.* 1983).

TxA_2 is produced from activated platelets and is a PGI_2 antagonist, having platelet aggregatory and vasoconstrictor properties (Hamburg *et al.* 1975). PGI_2 and TxA_2 oppose each other through regulation of adenylate cyclase in the platelet (Tateson *et al.* 1977), therefore TxA_2 may also have a role in these disorders. Both these substances are highly unstable and are usually measured as their stable metabolites. Prostacyclin's major metabolite is 6-keto-$PGF_{1\alpha}$, and thromboxane is converted to its stable hydration product thromboxane B_2 (TxB_2).

Measurement of PGI_2 metabolites has been, and remains, a subject of great controversy. Initial work on 6-keto-$PGF_{1\alpha}$ by radioimmunoassay (RIA) suggested that levels in normal subjects were of the order 70–100 pg/ml (Mitchell 1978), and this was supported by gas chromatography–mass spectometry (GCMS) which suggested similar levels (Hensby *et al.* 1979). However, Blair *et al.* (1982) using negative ion GCMS, showed that the absolute values for 6-keto-$PGF_{1\alpha}$ were <5 pg/ml, and they concluded that PGI_2 could not be a circulating hormone in man as previously thought. This does not preclude a role for PGI_2 functioning as a local hormone in the regulation of platelet–vessel wall interaction. Changes in levels of its stable metabolites must reflect changes in production, it is still therefore valuable to measure these metabolites to elucidate the role of prostacyclin in disease. RIA has also been discredited by varying 'normal' values due to differences in methodology and antibody sensitivity (Vinnikka & Ylikorkala 1982). While RIA cannot give absolute values for PGI_2 metabolites, the assay can still produce accurate comparative values.

Much improved RIA methods have been developed recently with sensitivities and normal levels much closer to that obtained by GCMS. RIA therefore, can still yield much valuable and accurate data provided proper controls are included and validation performed (Salmon 1983), and have many advantages over GCMS, as it is relatively sensitive, specific and can cope with large numbers of samples. For these reasons RIA is probably the method of choice from routine measurements (Belch *et al.* 1983; Salmon 1983).

There is little information on the normal levels of PGI_2 and TxA_2 in pregnancy, and since they may be implicated in disease processes, it is necessary to know the normal ranges. Lewis *et al.* (1980) published levels of 6-keto-$PGF_{1\alpha}$ and showed an elevation in late normal pregnancy and the puerperium. Bolton *et al.* (1981) recorded serial measurements throughout 12 normal pregnancies, and found a peak at 18–22 weeks gestation with a subsequent reduction towards term. Both of these studies were reported before the work by Blair *et al.* (1982) and suggested normal ranges of 80–200 pg/ml for 6-keto-$PGF_{1\alpha}$. These studies are still quoted as normal ranges despite subsequent advances in knowledge and assay techniques. In view of these advances and the conflicting reports of Lewis *et al.* (1980) and Bolton *et al.* (1981), the aim of our study was to determine the comparative values of PGI_2 and TxA_2 metabolites throughout normal pregnancy and the puerperium, using a RIA which has been shown to be sensitive, specific and reproducible for PGI_2 metabolites (McLaren *et al.* 1985).

Patients and methods

The study included 155 women; 44 normal non-pregnant, 29 women in the first trimester of pregnancy, 31 in the second trimester, 29 in the third trimester, and 21 women on the third day following delivery. All pregnancies were uncomplicated and no subject had taken any aspirin or similar preparations for at least 2 weeks before blood sampling.

Venous blood was taken without stasis into an anticoagulant mixture consisting of 3·8% w/v trisodium citrate containing 3×10^{-5} M indomethacin and 10^{-4} M adenosine (9 volumes of blood to 1 volume anticoagulant), and then centrifuged at 4 °C for 20 min at 3000 r/min. Plasma prostacyclin metabolite (PGI_2M) was measured on unextracted plasma by radioimmunoassy as described previously (Belch *et al.* 1983; McLaren *et al.* 1985). Lower limit of sensitivity of the assay is 5 pg/ml, recovery of added 6-keto-$PGF_{1\alpha}$ was 95 (SD 9), intra-assay variation is 4% and interassay variation 9%. The assay was validated by hydrolysing known quantities of PGI_2 in buffer, and comparing this with the same quantities of 6-keto-$PGF_{1\alpha}$ measured by the same assay, this produced a parallel standard curve (McLaren *et al.* 1985). Validation was also performed *in vivo* by measuring PGI_2M in normal volunteers infused with PGI_2 (Belch *et al.* 1983) where measured plasma PGI_2M correlated well with the rate of the infusion. Furthermore patients taking non-steroidal anti-inflammatory agents had undetectable PGI_2M levels after treatment. TxB_2 was measured in unextracted plasma, by a RIA with a lower limit of sensitivity of 20 pg/ml, intra-assay variation was 4%, and interassay variation 10%. It is a debatable subject in the field of RIA, whether plasma samples should be extracted or not, since many extraction procedures can add further impurities (Greaves & Preston 1982), which can produce detectable levels of PGI_2M in distilled water blanks subjected to the same procedure. The assay we used has been shown to be sensitive, reproducible and specific for measurement of PGI_2M directly in unextracted plasma, avoiding the technical difficulties associated with extraction procedures (McLaren *et al.* 1985). Statistical analysis was by the Wilcoxon rank sum test.

Results

Results for PGI_2M are shown in Fig. 1, and for TxB_2 in Fig. 2. We found a significant difference in PGI_2M levels in the first trimester ($p<0\cdot01$) when compared with those in the non-pregnant group. While there were no significant differences between non-pregnant values and those in the second or third trimesters, we noted a trend towards lower concentrations of PGI_2M on the third postnatal day, but this did not reach significance. Levels of PGI_2M were significantly lower in the second and third trimester than in the first trimester group. There was a progressive reduction in plasma TxB_2 concentrations from the second trimester, through the third trimester and into the puerperium. Table 1 gives a fuller statistical analysis.

Discussion

Despite using larger numbers we did not confirm the work of Lewis *et al.* (1980) who showed a

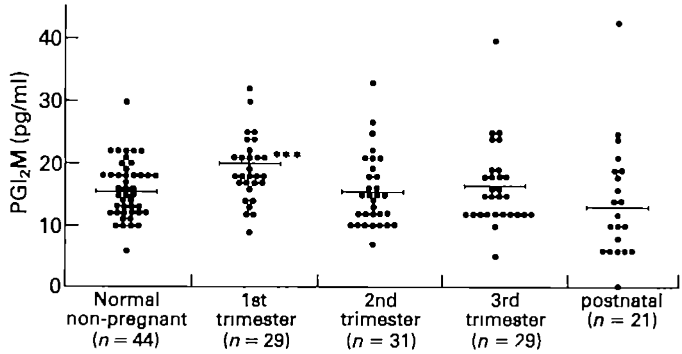

Fig. 1. Plasma concentrations of prostacyclin metabolite (PGI_2M) (pg/ml) in normal pregnancy and the puerperium ***$P<0\cdot01$

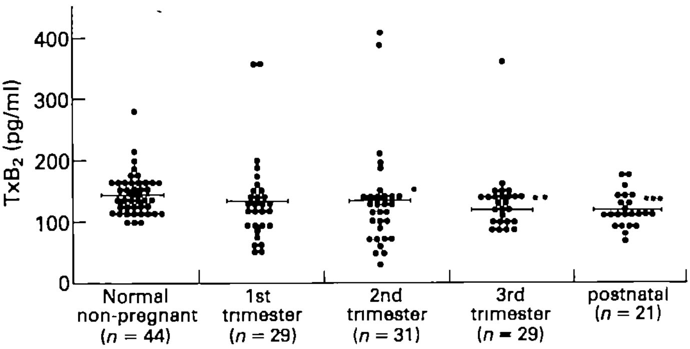

Fig. 2. Plasma concentrations of thromboxane B_2 (TxB_2) (pg/ml) in normal pregnancy and the puerperium. *$P<0\cdot05$, **$P<0\cdot02$; ***$P<0\cdot01$.

Table 1. Plasma levels of prostacyclin metabolite (PGI_2M) and thromboxane B_2 (TxB_2) in non-pregnant women, the three trimesters of pregnancy and the puerperium

	Non-pregnant	1st trimester	2nd trimester	3rd trimester	Postnatal
PGI_2M	15·9 (0·68)	19·9 (0·96)***	15·5 (1·05)	16·4 (1·22)	13·6 (1·99)
TxB_2	142 (4·9)	131 (14·2)	133 (14·9)*	123 (10·7)**	119 (6·3)$^{*\ **}$
n	44	29	31	29	21

$^{***}P<0{\cdot}01$, $^{**}P<0{\cdot}02$, $^{*}P<0{\cdot}05$ compared with non-pregnant; $^{***}P<0{\cdot}05$, $^{**}P<0{\cdot}01$, $^{*}P<0{\cdot}005$ compared with 1st trimester.
Results are mean (SEM) values.

higher concentration of 6-keto-$PGF_{1\alpha}$ in late pregnancy and the puerperium. We could not confirm the work of Bolton *et al.* (1981) as our peak levels of PGI_2M occurred in the first trimester, and not in mid-pregnancy as they reported, although they did not record levels before 14 weeks gestation.

We found a significant difference in the first trimester compared with values in the non-pregnant and second and third trimesters. This early increase may be involved in the physiological vasodilation and insensitivity to angiotensin II (Gant *et al.* 1973) which are characteristic of early pregnancy.

It has recently been shown that trophoblast from early pregnancies has a high capacity to synthesize PGI_2, and it has been suggested that colonization of maternal blood vessels by trophoblast is facilitated by PGI_2, which may prevent platelet aggregates from halting this process (Lewis 1982). This theory might explain our findings of elevated PGI_2M levels in early pregnancy. Failure of this response may possibly result in threatened or spontaneous abortion, and may even lead on to fetal growth retardation in later pregnancy, a condition where low PGI_2 metabolites have previously been recorded (Jogee *et al.* 1983; Stuart *et al.* 1981).

Theoretically one might expect high levels of PGI_2 in late pregnancy, due to the potential for increased production from the uterus and fetoplacental circulation unit. We have not found any increased levels at this stage. This may be explained by the findings of Remuzzi *et al.* (1981), who found a reduced level of prostacyclin-stimulating factor in late normal pregnancy, possibly a homeostatic mechanism. Since the capacity to produce PGI_2 is increased at this stage, less prostacyclin-stimulating factor is required, and PGI_2 levels would remain constant as we have described. Conversely when the ability to produce PGI_2 is low, as in pregnancy-induced hypertension, prostacyclin-stimulating factor rises in an attempt to increase PGI_2. This change has also been noted by Remuzzi *et al.* (1981). In the postnatal group we observed a trend towards reduced levels which contradicts the work of Lewis *et al.* (1980). Our sampling was performed only on the third postnatal day, while Lewis *et al.* (1980) sampled between the first and seventh postnatal days. If many of the samples were obtained soon after delivery they may have a high 6-keto-$PGF_{1\alpha}$ level due to vascular injury. Also, increased in-vitro production of 6-keto-$PGF_{1\alpha}$ from sheep cervical tissue taken at parturition has been reported (Ellwood *et al.* 1981). Since the fetoplacental unit, which has enormous capacity to synthesize PGI_2, is removed at birth, a reduction in 6-keto-$PGF_{1\alpha}$ levels postnatally might be expected.

We have observed a progressive fall in plasma TxB_2 concentrations through pregnancy and into the puerperium. This may reflect increased platelet stability, or the diversion of TxB_2 precursors into the formation of other prostaglandins, such as PGD_2 or PGE_1. Other possible explanations of this may be related to a change in activity of thromboxane synthetase or decreased substrate availability, but further studies are required to elucidate this. We noted several very high levels of TxB_2 (Fig. 2) which we cannot explain; they were levels normally associated with traumatic venepuncture or haemolysis, but we discarded all samples in which either of these problems were apparent. We would suggest that these may be due to subclinical trauma at the time of venepuncture with resultant platelet activation.

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Catecholamine responses to changes in posture during human pregnancy

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Summary. Human pregnancy may induce changes in the sensitivity of the cardiovascular system to endogenous catecholamines. This was investigated in multigravid women with little likelihood of unsuspected vascular disease. The responses of blood pressure, pulse rate, plasma noradrenaline and adrenaline to a change in posture from semi-recumbency to standing were assessed in six normotensive women at 36 weeks gestation and in six non-pregnant control subjects. Standing for 10 min caused a surge in blood pressure, pulse rate and plasma noradrenaline in non-pregnant women. The pregnant women, whose basal levels of noradrenaline were higher than those in non-pregnant women, showed a slower noradrenergic response to postural change, and this response had less effect upon the cardiovascular indices. Blood pressure dropped immediately on standing and pulse rate remained unaffected throughout. It is suggested that some women may maintain a non-pregnant level of pressor sensitivity during pregnancy and thereby become hypertensive.

In normal individuals the levels of systolic and diastolic blood pressure are retained within a relatively narrow range. The catecholamines of the sympathetic nervous system and adrenal medulla are involved in this control particularly in the maintenance of blood pressure against the force of gravity when an individual assumes an upright posture. Noradrenaline and adrenaline cause a change in peripheral resistance via alpha-receptors in the arteries, an increase in cardiac output via the cardiac beta-receptors, an alteration in venous tone through their alpha-receptors; the circulating concentrations of angiotensin II and aldosterone are influenced secondary to a beta-receptor effect in the kidneys (Kuchel 1983). Because of these actions a possible relation between the catecholamines and hypertension has been sought both in those suffering from essential hypertension and in women developing pregnancy-induced hypertension. Two main investigative approaches have been used: in one the circulating levels of the catecholamines have been measured in women with essential hypertension and pregnancy-induced hypertension and compared with concentrations found in normotensive women; in the other approach noradrenaline has been infused into similar groups of patients and the effect upon their blood pressure determined. The hypothesis behind the first approach is that pregnant women may have an enhanced activity of their adrenergic system causing increased peripheral resistance and hence hypertension (Zuspan 1979); however, two reports have suggested that basal circulating noradrenaline concentrations are the same in patients with pregnancy-induced hypertension as in normal

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pregnant women (Davey *et al.* 1981; Pedersen *et al.* 1982) while two others found noradrenaline levels to be lower in women with pregnancy-induced hypertension (Tunbridge & Donnai 1981; Natrajan *et al.* 1982). The second approach tests the hypothesis that hypertensive women have an increased sensitivity to catecholamines. Patients with essential hypertension but having normal noradrenaline levels have shown inappropriately increased noradrenaline reactivity (Philipp *et al.* 1978); infusing noradrenaline into normal pregnant women causes the same increase in blood pressure as when infused into non-pregnant women but promotes higher blood-pressure levels in patients with pregnancy-induced hypertension (Talledo *et al.* 1968). In these studies the amounts of noradrenaline infused were usually large and caused circulating concentrations well outside of the normal range before achieving recognizable effects on blood pressure (Cryer 1980). An alternative possibility, not so far investigated, is that some pregnant women increase their responsiveness to normal levels of circulating catecholamines following physiological stimuli and hence develop hypertension. But to investigate this possibility we had first to determine any differences in blood pressure, pulse rate and catecholamine responses between healthy non-pregnant and normal pregnant women using a change in posture to stimulate the release of noradrenaline; these data we report here.

Patients and methods

Subjects

Six normotensive, healthy, non-pregnant women aged between 27 and 35 years (mean 33 years) were recruited to the study. Each had attended our pre-conception clinic, had had uncomplicated pregnancies resulting in living children and the mean interval since their last delivery was 2 years (range 1–5 years). None was using an oral contraceptive agent at the time of testing or in the recent past. Six normotensive, healthy pregnant women were also recruited from our routine antenatal clinic; they had a mean age of 30 years (range 21–33 years). Each had had previous successful pregnancies resulting in live children, their present pregnancies were uncomplicated and all subsequently gave birth to live healthy babies at term. The tests were undertaken during the 36th week of gestation.

Protocol

The patients were requested to attend between 11.00 and 13.00 hours having eaten normally at breakfast-time; they were asked not to drink caffeine-containing liquids nor to smoke during the hour preceding their arrival nor were these allowed during the course of the investigations. On arrival each was asked to rest in a semi-recumbent position on a comfortable bed in a quiet room. After 30 min a cannula was placed in an antecubital vein, a blood sample obtained and the cannula left in position to obtain subsequent blood samples without a tourniquet; pulse rate and blood pressure were determined in the opposite arm. The patients then remained at quiet rest for a further 30 min during which pulse rate and blood pressure were measured every 10 min; at the completion of this second 30 min of rest another blood sample was obtained. The final resting values for pulse rate, blood pressure and plasma catecholamines were used as the 'basal' levels. The patients were then asked to stand upright for 10 min during which repeat measurements were made and blood samples otained at 2-min intervals beginning 1 min after assuming the upright position. The women then resumed their semi-recumbent posture and these observations and blood samples repeated at 5-min intervals for a further 15 min.

The project had the approval of the local ethical committee and informed consent was obtained from each individual.

Blood samples

These were placed into heparinized tubes which had been pre-cooled in an ice-bath and then centrifuged at 4°C: the plasma was stored in liquid nitrogen until assayed for the catecholamines.

Blood pressure and pulse rate

Both were measured by an HED Digital Electronic Sphygmomanometer (HED Electronic Systems Ltd, Harrogate, UK). This had been adjusted to accept the fourth Korotkoff sound as the diastolic pressure and calibrated against intra-arterial pressure measurements undertaken in non-pregnant patients requiring cardiac catheterization.

Catecholamine assay

Plasma samples were incubated with catechol-O-methyltransferase and either S-(^{3}H) or S-(^{14}C) adenosyl-L-methionine and had their catecholamines converted to labelled meta-adrenalines (Brown & Jenner 1981). The ^{14}C activity allows for correction for efficiency of methylation and recovery after extraction. For noradrenaline, the assay sensitivity was 0·08 nmol/l, the intra-assay and interassay coefficients of variation were 7·5% and 9·5% respectively. The corresponding figures for adrenaline were 0·02 nmol/l, 10·8% and 12·0% respectively.

Statistics

Changes in all measurements from the basal determinations within patients were analysed using paired *t*-tests; differences between the pregnant and non-pregnant patients were analysed using the Mann–Whitney *U*-test (Armitage 1971).

Results

Pre-basal blood pressure variation

In the 30 min of rest after placement of the venous catheter each patient had four blood pressure measurements; the mean within-patient standard deviation (SD) for systolic blood pressure was 4 mmHg for the non-pregnant women and 6 mmHg for the pregnant women. The corresponding SD values for diastolic pressure were 5 and 4 mmHg respectively.

Basal measurements

The pregnant women had a statistically significantly higher mean basal systolic blood pressure than the non-pregnant women but in both groups it remained within the normal range. The mean diastolic pressure was also higher but the difference did not achieve statistical significance. If the readings were combined and expressed as the mean arterial pressure then this measurement had a higher mean value in the pregnant women who also displayed a significantly higher pulse rate. The plasma concentrations of both catecholamines significantly increased in the pregnant group. These data are summarized in Table 1.

Effect of standing

Systolic blood-pressure. Immediately upon standing the non-pregnant women exhibited a marked increase which was sustained over the 10 min. Such was not the case for the pregnant group who displayed an initial decrease in systolic pressure followed by an increase which achieved a similar level to that in the non-pregnant women for the final 5 min of standing (Fig. 1; Table 2).

Diastolic blood pressure. The initial pressure changes were similar to the systolic responses with the non-pregnant women diplaying an immediate and sustained increase but the pregnant women showing an initial decrease in the diastolic pressure; the diastolic pressure regained the basal level thereafter. The effect was that the mean diastolic pressure was significantly lower in the pregnant group as was their mean arterial pressure (Fig. 1; Table 2), though not all patients followed these mean trends.

Pulse rate. The heart rate responded more slowly to change in posture. In non-pregnant women there was no obvious effect at 1 min but

Table 1. Basal cardiovascular and catecholamine measurements

Measurement	Non-pregnant women (n = 6)	Pregnant women (n = 6)	Significance of difference (P)
Blood pressure (mmHg)			
Systolic	106 (6)	122 (9)	<0·01
Diastolic	72 (10)	80 (7)	NS
Mean arterial	83 (8)	94 (6)	<0·05
Pulse rate (beats/min)	79 (5)	88 (9)	<0·01
Noradrenaline (nmol/l)	2·06 (0·48)	3·18 (0·62)	<0·05
Adrenaline (nmol/l)	0·15 (0·08)	0·33 (0·12)	<0·01

Measurements [mean (SD)] were made after 1 h of rest in a semi-recumbent position.

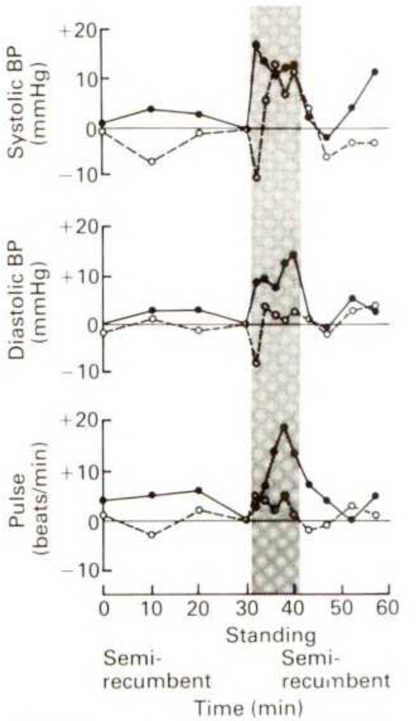

Fig. 1. Mean changes in blood pressure and pulse rate following changes in posture in six healthy non-pregnant women (●) and six healthy pregnant women (○) at 36 weeks gestation. The basal values from which these changes were recorded were those obtained at 30 min. The variability of measurements is indicated in Tables 1 and 2

by 5 min the average increase in rate of 15 beats/min was significant. The pregnant women had a much more variable response within individuals and the group as a whole showed no change in rate while standing (Table 2).

Noradrenaline. In both groups of women there was an immediate and sustained increase in plasma concentration. In the non-pregnant group the increase was more rapid, the peak values greater and achieved at about 5 min after standing whereas the pregnant women achieved their maximum levels at about 10 min (Fig. 2).

Adrenaline. The pattern of change in plasma concentrations differed in the two groups. The non-pregnant women had a tendency to increase their circulating concentrations whereas the pregnant women showed an immediate and significant decrease ($P<0{\cdot}02$) in adrenaline levels on standing with a variable pattern around the lower values thereafter. The average change over the period of standing did therefore differ between the two groups (Table 2).

Regaining recumbency

Systolic pressure. Both groups of patients regained their basal systolic blood pressure within 1 min of returning to the recumbent position but while this level was more or less maintained in the pregnant women the non-pregnant

Table 2. Cardiovascular and catecholamine changes on standing in six non-pregnant (N) and six pregnant women (P)

	1-min reading			10-min reading			Average within-patient change over 10 min		
Measurement	N	P	NvP	N	P	NvP	N	P	NvP
Blood pressure (mmHg)									
Systolic	18 (10)**	−10 (22)	*	13 (12)*	12 (19)	NS	14 (6)**	8 (9)	NS
Diastolic	9 (8)*	−8 (15)	*	15 (11)*	3 (8)	*	11 (8)*	1 (4)	*
Mean arterial	12 (4)**	−9 (17)	*	15 (11)*	6 (10)	*	12 (6)**	3 (3)	**
Pulse rate (beats/min)	3 (4)	5 (9)	NS	13 (11)*	1 (10)	*	12 (3)**	3 (7)	**
Noradrenaline (nmol/l)	0·78 (0·53)*	0·18 (0·48)	NS	1·12 (0·71)*	1·17 (1·04)*	NS	1·16 (0·45)**	0·76 (0·74)*	NS
Adrenaline (nmol/l)	0·12 (0·14)	−0·07 (0·04)*	**	0·10 (0·11)	−0·02 (0·08)	*	0·10 (0·16)	−0·02 (0·05)	*

Measurements were repeated at 2-min intervals during 10 min of standing and the basal values shown in Table 1 subtracted from each. The means (SD) of these differences at 1 min and 10 min are given together with the average within-patient mean and SD over the whole 10 min. The mean differences from basal achieving significance are shown by an asterisk; the non-pregnant versus pregnant (NvP) column uses an asterisk when the differences between non-pregnant and pregnant groups achieves significance. * $P<0{\cdot}05$; ** $P<0{\cdot}01$.

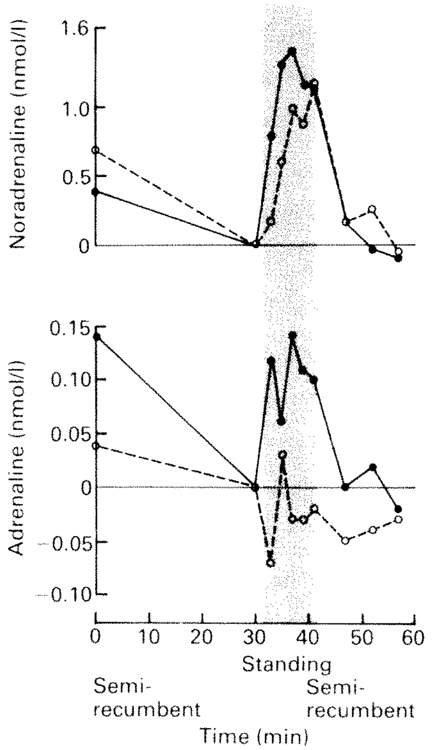

Fig. 2 Mean changes in plasma noradrenaline and adrenaline following changes in posture in six healthy non-pregnant women (●) and six healthy pregnant women (○) at 36 weeks gestation. The basal values from which these changes were recorded were those obtained at 30 min. The variability of measurements is indicated in Tables 1 and 2.

women increased their systolic pressure again to values similar to the peak standing values in some individuals (Fig. 1).

Diastolic pressure. The basal levels were rapidly achieved in both groups and did not alter much thereafter (Fig. 1).

Pulse rate. Little change was obvious in the pregnant women but the non-pregnant group had regained their basal levels within 10 min (Fig. 1).

Noradrenaline. In both groups concentrations had returned to the basal values within 5 min of returning to the resting position (Fig. 2).

Adrenaline. While the levels in the non-pregnant women returned to the basal values within 5 min the depressed levels found in the pregnant women on standing had not recovered even after 15 min of rest (Fig. 2).

Discussion

Assuming an upright position after resting in recumbency allows blood to pool in the veins of the legs. The reduced venous return to the heart causes a decrease in stroke volume and cardiac output which would result in a decrease in blood pressure; however, the baro-reflex stimulates a noradrenergic response which has three important effects: first it causes an increase in heart rate and improves cardiac contractility to maintain myocardial output; second it constricts the muscle fibres in the arteriolar walls thereby reducing the volume of the intravascular space and increasing peripheral resistance thus helping to maintain blood pressure; third, the neuronal discharge of noradrenaline leads to a rise in circulating concentration. Adrenaline is released from the adrenal medulla but appears to be less important in the maintenance of blood pressure during postural change though it has a vasodilatory effect on skeletal muscle and causes some stimulation of heart rate.

In our non-pregnant women systolic and diastolic blood pressures both increased immediately on standing, as did noradrenaline concentrations. As the pulse rate was unchanged, one can infer that the raised blood pressure was caused by a briskly enhanced peripheral resistance related to the increase in noradrenaline. By 5 min the heart rate had accelerated and blood pressure remained high; this has also been described by others (Ziegler *et al.* 1977). Noradrenaline levels and pulse rate were decreasing by 10 min and if standing had continued these trends would have presumably led back to basal blood pressures. Other studies of stimulation by postural change (Whitfield *et al.* 1980) have not found a change in blood pressures at 10 min but made no observations during the intervening period.

The pregnant women displayed an entirely different response to the change in posture. Both systolic and diastolic blood pressures decreased promptly upon standing while both pulse rate and noradrenaline levels were unchanged. This suggests that during late pregnancy the sympathetic system may be slower to respond to the drop in cardiac output that occurs on standing and allows the decrease in blood pressure to become more evident. It also seems that the vascular reaction to noradrenaline is diminished because while circulating levels eventually increase to the levels seen in non-pregnant women only systolic blood pressure achieves a change similar to the non-pregnant, while the diastolic blood pressures in pregnancy simply return to basal levels. These changes are probably the result of vasoconstriction since the heart rate seems unaffected, though the decrease in circulating adrenaline may have been a counter-influence upon heart rate. A recent study has shown that in pregnant women, standing causes rapid cyclical rises in heart rate and falls in blood pressure (Schneider *et al.* 1984).

Several studies have failed to find any convincing relation between noradrenaline concentrations and the level of blood pressure in women with essential hypertension or pregnancy-induced hypertension (Pedersen *et al.* 1982) and it seems unlikely that these disorders are caused by an increased circulating level of a pressor agent. The 'roll-over' test causes variable changes both in blood pressure and the plasma levels of noradrenaline and the relation of one to the other is poor (Tunbridge & Donnai 1983). Our data may offer an alternative explanation: that during normal pregnancy there is a reduced adrenergic responsiveness to change in posture both in terms of the speed of increase in circulating noradrenaline levels and the absolute concentrations of adrenaline achieved. The effect is that blood pressure is maintained at an adequate level but by a modified response: peripheral resistance probably increases but heart rate does not. While these changes may seem slight it must be remembered that in late pregnancy plasma volume is expanded by about 40%, and renin, angiotensin and aldosterone levels are increased (Weinberger *et al.* 1976). The possibility arises therefore that if adrenergic responsiveness is retained by pregnant women at the level found in non-pregnant women then they could become hypertensive. This might be particularly relevant to women during their first pregnancy and we are currently investigating this possibility.

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Plasma catecholamines and modes of delivery: the relation between catecholamine levels and in-vitro platelet aggregation and adrenoreceptor radioligand binding characteristics

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Summary. Catecholamines were measured in maternal venous, and mixed umbilical cord blood. Maternal catecholamines were significantly ($P<0{\cdot}01$) reduced by epidural analgesia with a 36% reduction in noradrenaline and a 33% reduction in adrenaline. Fetal catecholamines were elevated at birth with a 3–8 fold increase in noradrenaline but not adrenaline during spontaneous vaginal delivery. The lowest fetal catecholamines were obtained in the group delivered under epidural analgesia; lower plasma catecholamines were not associated with adverse respiratory effects. Fetal platelets showed impaired α_2-adrenoceptor function with absent aggregatory responses to adrenaline *in vitro*. The defect in platelet function was unlikely to be related to changes in the number of fetal platelet α-receptors or to changes in receptor affinity for adrenaline, as fetal platelets failed to aggregate to adrenaline from deliveries with high and low cord blood catecholamines.

Birth is one of the most stressful periods of life during which time the highest recorded values of plasma catecholamines have been obtained from umbilical cord blood at the time of vaginal delivery (Natai & Yamada 1978). The aims of the present study were to document maternal and fetal plasma catecholamine concentration associated with different modes of delivery and to examine the effects of the elevated catecholamines at birth on maternal and fetal α-adrenoceptor number, affinity and function.

Subjects and methods

Paired blood samples (40–60 ml) were obtained from mothers by venepuncture and fetal samples from mixed cord blood after delivery of the placenta. The women were aged 19–40 years and had been normotensive during pregnancy which ended at between 38 and 42 weeks; no aspirin-like drugs had been ingested for 2 weeks. The Apgar score was obtained from the case notes and the mean of the 1- and 5-min values taken.

Plasma catecholamines

Catecholamine samples were obtained from 41 women. Ten had a vaginal delivery with analgesia by N_2O and pethidine, and six had a vaginal delivery with epidural analgesia. Twenty-four women were delivered by caesarean section, 16 with epidural and eight with general anaesthesia. Fetal samples were obtained from mixed cord blood in nine of the 10 vaginal deliveries with pethidine and nitrous oxide analgesia and four of those who had epidural analgesia. In the caesarean section group fetal blood samples were obtained in 13 out of the 16 women who had epidural analgesia and in all eight who had general anaesthesia. In four of the women who had a caesarean section fetal umbilical artery and vein blood samples were obtained to allow calculation of the extraction of catecholamines by the placenta. Samples were collected into iced heparinized containers and centrifuged within 10 min at 4°C to separate the plasma which was stored at −70°C. Adrenaline and noradrenaline assays were peformed by a sensitive specific radioenzymatic assay with an interassay coefficient of variation of 12% (Da Prada & Zurcher 1976).

Platelet aggregation

Platelet-rich plasma was prepared from a further group of six women who had a spontaneous vaginal delivery with N_2O and pethidine analgesia and six who were delivered by caesarean section under epidural analgesia. Venous blood was centrifuged at 180 *g* for 10 min at 20°C and platelet aggregation was monitored *in vitro* by a turbidometric method (Born & Smith 1970) using platelet-poor plasma from the same patient as the reference sample for maximum light transmission in the fully aggregated specimen. Aggregation was performed with 450 μl of platelet-rich plasma and 50 μl of aggregating agent. The aggregating agent used was (−)adrenaline bitartrate (Sigma 1 μM–1 mM) prepared from stock solutions of 1 mM which were stored at −70°C. The adrenaline was dissolved in 0·9% saline with 1 mM ascorbic acid. All dilutions of adrenaline were made using the 0·9% saline/1 mM ascorbic acid solutions diluent. The maximum rate of adrenaline aggregation was obtained by drawing a tangent to the line of the greatest change in the slope of the aggregometer tracing and this was plotted against the log of the adrenaline concentration to obtain the concentration required to produce 50% of the maximal rate of aggregation (IC_{50}).

α-Adrenoceptor binding assay

Radioligand binding studies were performed on 12 maternal samples (four spontaneous vaginal deliveries with N_2O and pethidine analgesia and eight caesarean sections, six with epidural and two under general anaesthesia). Fetal samples were obtained from mixed cord blood, six of the spontaneous vaginal deliveries, nine delivered by caesarean section under epidural and four delivered by caesarean section under general anaesthetic. The platelets were separated from the platelet-rich plasma by centrifugation at 1,700 *g* for 10 min at 20°C and resuspended in 0·1% (w/v) EDTA 150 mM NaCl pH 7·5. Platelet cell density was estimated by a Coulter Counter and cell concentration adjusted to 100 × 10^{-9} cell/l. Incubations were performed at 25°C for 20 min in triplicate with six concentrations of [^{3}H]-yohimbine between 1 and 20 nM (Daiguji *et al.* 1981). Non-specific binding was defined by 1μM phentolamine The incubation was terminated by filtration with 20 ml of ice-cold buffer (50 mM Tris, 150 mM NaCl, pH 7·5) through a millipore multiport filtration apparatus over Whatman glass filters (GFC) (Alexander *et al.* 1978). The bound radioactivity on the filters was determined by liquid scintillation counting at 35% efficiency.

Statistical methods

The results are represented as mean (SD) and group comparisons were made by Student's *t*-test. Significance was taken as $P<0{\cdot}01$ to make allowance for multiple comparisons. The placental extraction of catecholamines was calculated by the arteriovenous difference divided by the artery plasma catecholamine concentration. The equilibrium binding data were analysed by least-squares fitting of the plot of free/bound *vs* free with correlation coefficients >0·9 for all data sets. As individual error estimates were available statistical analysis incorporated these by a weighted analysis of variance.

Results

Plasma catecholamines

Catecholamine concentrations for mothers and babies are shown in Figs 1 and 2 respectively. The fetal noradrenaline levels were significantly higher than the maternal values in the group delivered by spontaneous vaginal delivery [15·7 (17·4) *vs* 4·64 (2·99) nM, $P<0{\cdot}01$] but there were no differences in the plasma adrenaline levels [0·93 (1·06) *vs* 0·54 (0·31) nM]. There were no correlations between fetal and maternal plasma catecholamine levels for either adrenaline (r = 0·50, $P<0{\cdot}16$) or noradrenaline (r = 0·51, P =0·18).

The type of analgesia affected the levels of catecholamines in both mothers and babies. In the women who had a spontaneous vaginal

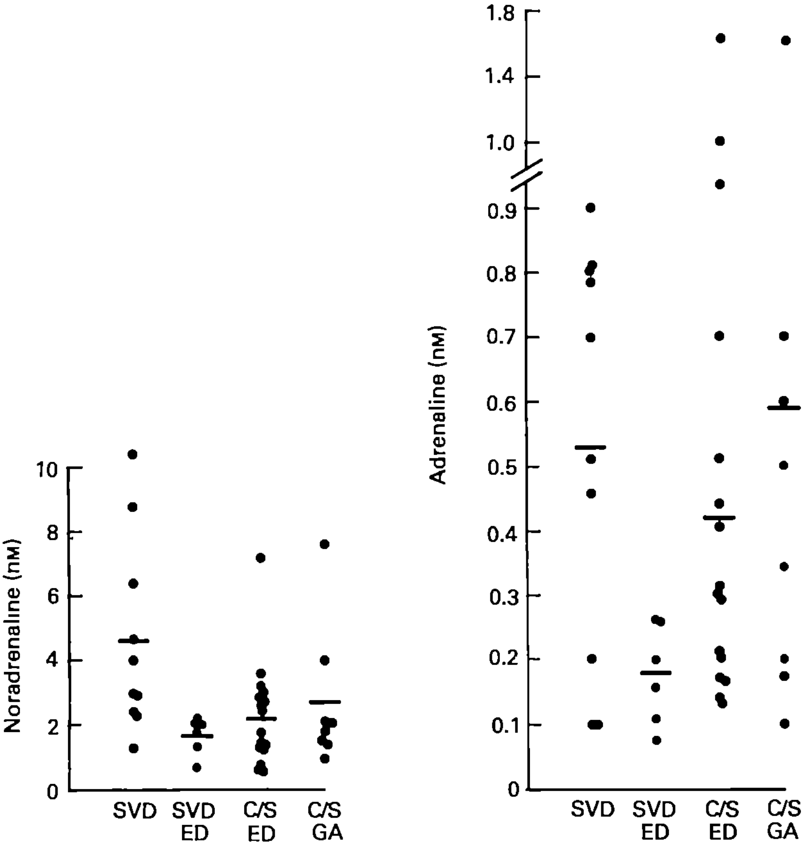

Fig. 1. Maternal catecholamines by mode of delivery. Individual values are shown and the mean is indicated by a horizontal bar. SVD, Spontaneous vaginal delivery with N_2O pethidine, SVD ED, spontaneous vaginal delivery with epidural; C/S ED, caesarean section with epidural analgesia; C/S GA, caesarean section with general anaesthesia

delivery, epidural analgesia resulted in a lowering of noradrenaline levels from 4·64 (2·99) to 1·71 (0·60) nM and adrenaline from 0·53 (0·31) to 0·18 (0·07) nM ($P<0·01$). A similar reduction in plasma noradrenaline was seen in those patients who had caesarean section under epidural analgesia compared with spontaneous vaginal delivery with N_2O and pethidine analgesia [2·22 (1·63) *vs* 4·64 (2·99) nM, $P<0·01$]. Maternal catecholamines after caesarean section with general anaesthesia but without epidural analgesia were not significantly different from the levels in the group with spontaneous vaginal delivery.

Fetal catecholamines were also affected by the mode of delivery (Fig. 2) with the lowest values occurring in those babies born by caesarean section under epidural analgesia. The mean fetal noradrenaline level was significantly higher [15·70 (17·40) nM] after spontaneous vaginal delivery with N_2O and pethidine analgesia than after caesarean section with epidural analgesia [5·08 (8·07) nM, $P<0·01$] but similar to that after caesarean section under general anaesthesia There was also no significant difference in fetal levels of adrenaline between the spontaneous vaginal deliveries [0·90 (1·06)] and caesarean section with epidural analgesia [0·88 (1·45)].

Umbilical artery and vein catecholamines were obtained from four placentas in the caesarean section group. The mean umbilical artery levels of noradrenaline and adrenaline were 14 (4) and 3 (1) nM respectively and the corresponding umbilical vein levels were 3 (3) and 0·3 (0·1) respectively. The net extraction of noradrenline was 85 (9)% and adrenaline 91 (5)%. Thus artery blood catecholamines were high despite the lower vein blood levels in this group. Most of the babies had high Apgar scores and were breathing spontaneously at 5 min;

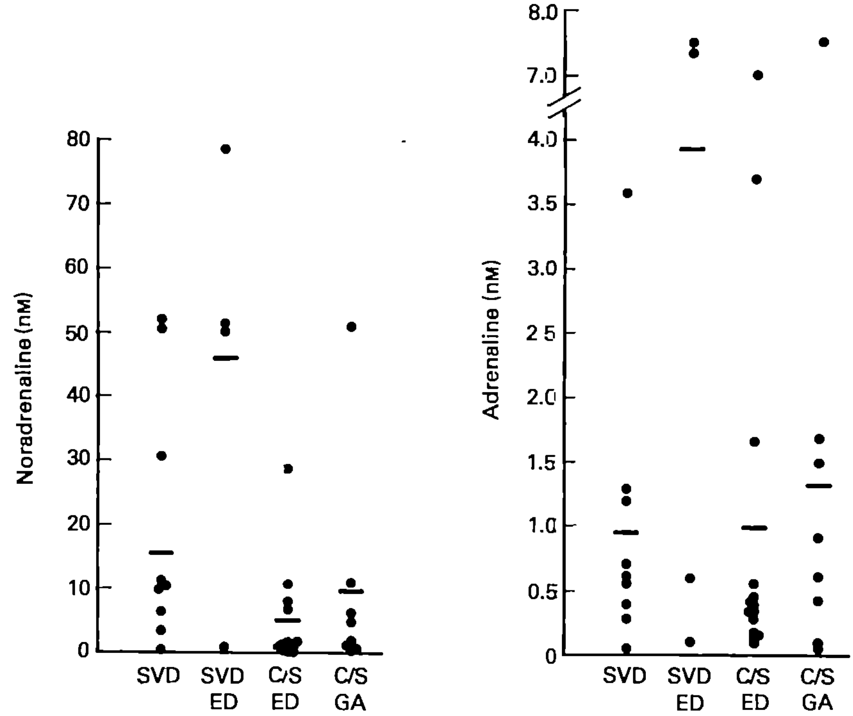

Fig. 2. Fetal catecholamines by mode of delivery, abbreviations as in Fig 1

there was no clear relation between the catecholamine levels and the Apgar score. In particular the highest fetal catecholamines were associated with neither high nor low Apgar scores.

Platelet aggregation

In-vitro aggregation of fetal platelets did not occur over the dose range 1 µM–1 mM as shown in Fig. 3 from babies born vaginally ($n = 6$) or by elective caesarean section under epidural analgesia ($n = 4$). This compares with the response of maternal platelets to adrenaline with a dose related increase in platelet aggregation. The mean concentration of adrenaline required to produce 50% maximal aggregation was 0·28 (0·29) µM for women in the vaginal delivery group and 0·12 (0·39) µM in women delivered by caesaean section with epidural analgesia ($P<0·09$, NS).

Platelet adrenoceptor binding

The platelet binding characteristics differed between the maternal and fetal groups. In view of the small numbers in the maternal data set the subgroups were combined as no apparent differences between subgroups were seen and they can be identified in Fig. 4, analysis of the binding data indicated a single binding site with non-specific binding accounting for 30–50% of total binding. There were differences in binding capacity between mothers and babies in the epidural/caesarean section group [47·72 (10) *vs* 30·50 (6·92) $P<0·01$] fmol/10^8 platelets respectively. The platelets from the babies with the highest catecholamine levels showed a significant decrease in the affinity of the α_2-receptor for the radiologand agonist [^{3}H]-yohimbine. The K_D was 12·16 (7·29) nM in the fetal group compared with 1·79 (1·29) nM in those born by epidural caesarean section ($P<0·01$). In the mothers there was no differences in K_D between the groups.

Discussion

Catecholamine levels differed with the type of delivery for both mothers and babies. The lower plasma noradrenaline concentration after epidural analgesia is consistent with blockade of sympathetic function of afferent and efferent pathways at a spinal level (Halter *et al.* 1977).

Fetal catecholamines also varied according to the type of delivery, the lowest concentration being observed in those babies born by caesarean section under epidural analgesia. Fetal catecholamines were not reduced by epidural analgesia alone (although the number of subjects in this group was small), or by caesarean section with general anaesthesia. The dominant response to birth stress was an increase in noradrenaline, in agreement with other authors

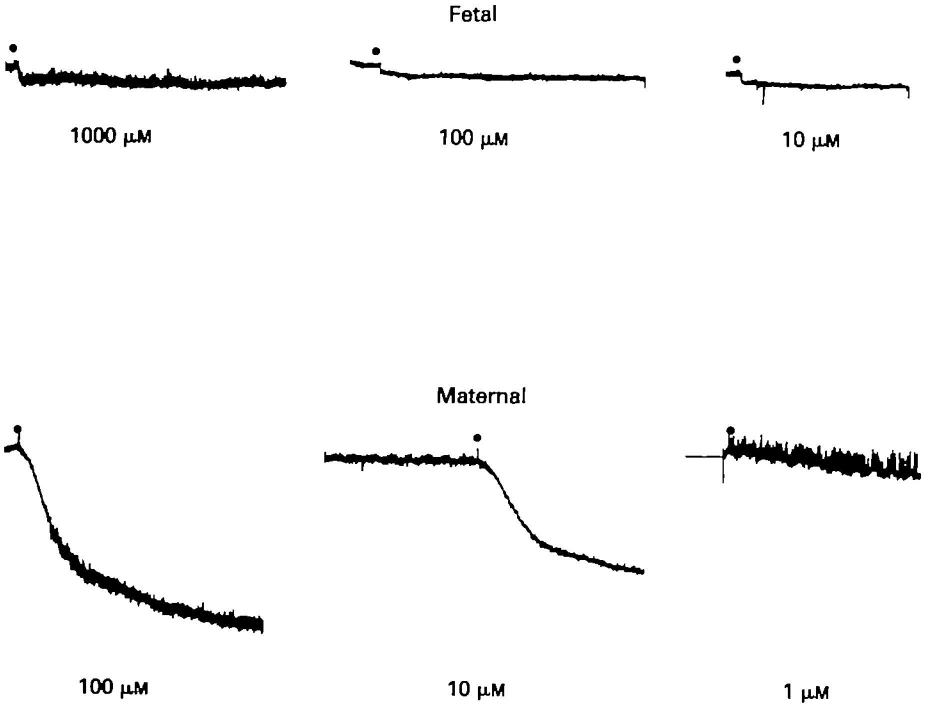

Fig. 3. Representative tracings from the fetal and maternal aggregation responses to adrenaline-induced aggregation, with lack of aggregation in the fetal sample at the highest concentration (1000 μM).

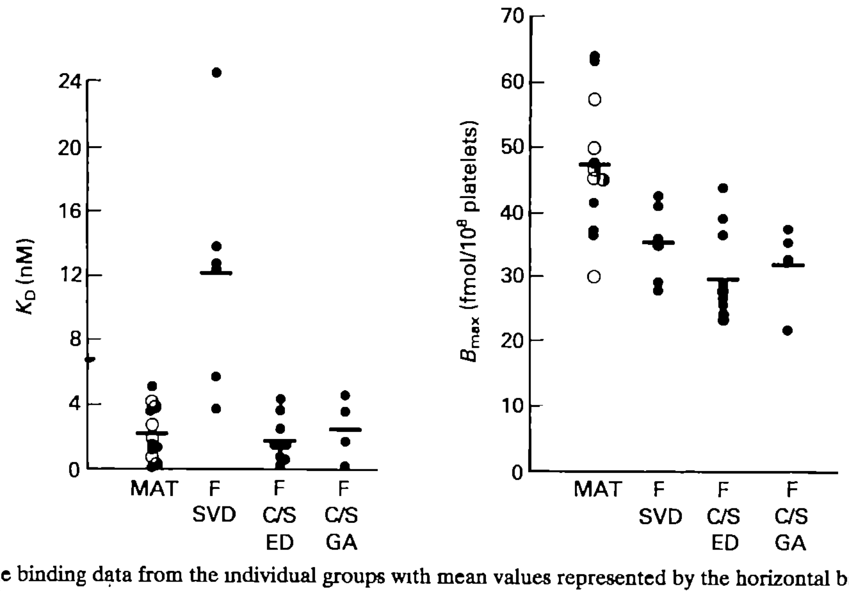

Fig. 4. The binding data from the individual groups with mean values represented by the horizontal bar, for the maternal (MAT) data (○ SVD, ● C/S ED, ◑ C/S GA), for the fetal (F) data, abbreviations as in Fig 1.

(Natai & Yamada 1978; Puolaka *et al.* 1983, Bistoletti *et al.* 1983). The reduction in fetal catecholamines with caesarean section is consistent with the importance of head compression in increasing sympathoadrenal activity during labour (Lindgron 1981).

Adrenaline has been recently shown to be involved in the fluid resorption that occurs in the lung at birth due to activation of β_2-receptors which stimulate water transport (Brown *et al.* 1983). These receptors are believed to be activated physiologically by the elevated catecholamines and this is consistent with the observation that the lungs of babies born by caesarean section are heavier (Milner *et al* 1978). However, in this study the Apgar scores in babies born by caesarean section under epidural analgesia were among the highest and yet at the same time this group had the lowest catecholamine levels. Thus withdrawal of the maternal and fetal sympathetic tone with reduction in fetal catecholamines was not associated with a noticeable adverse respiratory effect. One reason for this could be that the catecholamines present in the artery blood were sufficient to activate the physiological mechanism. Further study of fetal lung function by more sensitive methods in babies with low catecholamines would be informative. A congenital platelet abnormality (Glanzmann's thrombasthenia) and platelet release defects, which occur in low frequency and are associated with absent adrenaline-induced aggregation, could not explain the present results as both primary and secondary responses to adenosine diphosphate are unimpaired.

Lack of fetal platelet aggregation, as shown by others (Corby & Schulman 1971; Ts'ao *et al.* 1976), is seen in both the high- and low-catecholamine groups implying that this lack of function is not due to desensitization of the adrenoceptors caused by the elevated catecholamine levels. The number of α_2-receptors on fetal platelets was reduced in babies compared with maternal platelets and the binding experiments were also influenced by the catecholamine levels. A high catecholamine level after spontaneous vaginal delivery was associated with an increase in K_D or a reduction in the affinity of the receptor for the radioligand [^{3}H]-yohimbine. This could either be a direct result of the high circulating catecholamines or secondary to the release of retained catecholamines from the platelets during the assay (Karliner *et al.* 1981).

The absence of platelet aggregation in response to adrenaline does not appear to be due to a modest reduction in receptor number as fetal platelets had a similar number of adrenoceptors to that observed in healthy adult males (Motulsky *et al.* 1983). The explanation for the failure of adrenaline-induced aggregation may involve post-receptor mechanisms and requires further study.

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Quantitative measurement of fetal blood flow using Doppler ultrasound

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Summary. Blood flow in the descending human fetal aorta and in the intra-abdominal portion of the umbilical vein was quantified using pulsed Doppler ultrasound in a longitudinal series of normal pregnancies, the accuracy of the method having been verified *in vitro*. The results obtained are in keeping with previous studies but indicate that, although the method is relatively simple, determination of absolute blood flow in these vessels has little clinical potential because of inherent measurement inaccuracies.

Principally due to inaccessibility, less is known about the regulation of blood flow in the human placenta than in any other organ (Rankin & McLaughlin 1979). The recent application of Doppler ultrasound to human fetal vessels (Fitzgerald & Drumm 1977) has opened up a new field of investigation and, using this technique, flow characteristics have since been described both on the fetal (Stuart *et al.* 1980) and maternal (Griffin *et al.* 1983) sides of the placenta. Also, by further refinement of the method, blood flow has been quantified in the fetal aorta (Eik-Nes *et al.* 1980) and in the intra-abdominal portion of the umbilical vein (Gill & Kossoff 1979).

As gestation progresses, differing physiological and pathological conditions affecting the fetus might be expected to alter fetoplacental blood flow, so its non-invasive measurement has obvious clinical potential. To this end, using a model, we set out to assess the accuracy of a pulsed Doppler ultrasound system, after which the equipment was used to study normal pregnancies. Each pregnancy was studied serially, all previously published data having been compiled using cross-sectional information.

Subjects and methods

Echoes returning from a moving reflector have an altered frequency with respect to the incident beam of ultrasound, and the resulting frequency shift (Doppler effect) is dependent on the speed and direction (i e. velocity) of the reflector. Red blood cells scatter ultrasound rather than reflect it, but the back-scattered signals also contain shifted frequencies dependent on the speed of cell movement (Atkinson & Woodcock 1982) The angle between Doppler beam and insonated vessel is of crucial importance if absolute velocity is to be calculated, since the shifted frequencies obtained are directly proportional to the cosine of this angle (see equation 1).

The equipment used was a Mark V Duplex Doppler Ultrasonic Sector Scanner (Advanced Technology Laboratories) which integrates a real-time two-dimensional image with a range-gated 3-MHz pulsed Doppler probe in a quasi-simultaneous format. A real-time picture of the vessel under study is obtained and the line of insonation of the pulsed Doppler probe adjusted so that it passes through the vessel at as small an angle as possible. The depth of the range gate is adjusted to bring the sample volume within the vessel walls. The shift in frequency caused by blood flow lies in the audible range and is amplified and passed to an audio output. The sample volume can be placed accurately within the

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vessel at the point where the maximum change in frequency is heard in a manner somewhat akin to tuning a radio receiver. Due to laminar flow maximum blood velocity occurs at the centre of the vessel. When the sample volume completely fills the lumen of the insonated blood vessel the mean Doppler-shifted frequency (Δf) displayed by the equipment is proportional to the mean red cell velocity. However, precise placement of the sample volume to fill the vessel lumen completely is most unlikely and, since the sample volume of the ATL is fixed at 2 mm×4 mm, the mean Δf output of the equipment was not used. Instead, the average maximum Δf (mean Δf_{max}) was measured from the time velocity waveform or sonogram which in turn was produced automatically by spectral analysis of the Doppler-shifted frequencies by the fast Fourier transform technique. Secondary analysis of the hard copy printout to obtain the mean Δf_{max} was facilitated by using the digitizing tablet of a Cardio 80 Mini-computer (Kontron Ltd).

A model was created to validate the technique and calibrate the equipment, after which the system was applied to the measurement of blood flow in the human fetal aorta and intra-abdominal portion of the umbilical vein. The model (Fig. 1) consisted of a 'phantom blood vessel' immersed in a water bath filled with double-distilled water and covered with a thin rubber diaphragm. Citrated human blood was pumped through the system by a pulsatile cardiothoracic pump (Travenol Laboratories). A graduated cylinder was placed at each end of the system to act as a reservoir and each flow rate was calculated as the mean difference in volume in the two reservoirs over 1 min. Five flow rates were each tested 10 times to check the stability of the pump.

Twenty-five different flow rates in the model were studied and each flow rate was examined twice, in opposing directions. Doppler's original formula was used:

$$\text{Equation 1} \quad \Delta f = \frac{2Fv \operatorname{Cos}\theta}{c}$$

where F is the transmitted frequency, v is the reflector velocity, and c is the propagation speed of sound in tissue (1540 m/s) and θ is the angle of insonation between beam and vessel. This angle (θ) was measured from a photograph of the two-dimensional scan image on which is superimposed the direction of the Doppler beam.

Since absolute flow in the model was measured via the graduated cylinders and the internal diameter of the 'phantom' blood vessel' was known (0·625 cm), true mean velocity through the model could be calculated. A linear regression equation was plotted of mean Δf_{max} against the true mean velocity as measured by the graduated cylinders and this when inverted was used to determine mean blood velocity *in vivo*.

Patients

Fifteen women (14 multiparae and one primigravida) who gave birth to normal infants after 37 weeks gestation were each scanned at fortnightly intervals from 28 weeks gestation Maturity in each case was confirmed by ultrasonography at 16 weeks amenorrhoea. Mean gestation at delivery was 39^{+6} weeks (range 37^{+6} to 41^{+6}) and mean birthweight was 3602 g (range 2860–4110). All pregnancies were considered

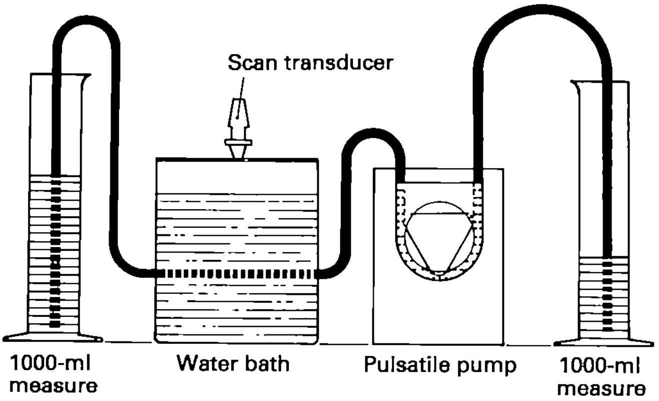

Fig. 1. Pulsatile model used to validate and calibrate the Doppler equipment.

clinically normal and all infants had Apgar scores of ≥9 at 5 min. The primigravida was the only patient to have an instrumental delivery, this being a lift-out forceps delivery under epidural analgesia for delay in the second stage of labour due to poor maternal effort.

At each scanning session Doppler signals were obtained from the descending fetal aorta just below the level of the diaphragm and from the umbilical vein just inside the fetal abdomen (IUV). The mean aortic diameter was measured on 10 frozen two-dimensional images as described by Eik-Nes *et al.* (1982*a*) using an EUB 25M linear array scanner (Hitachi). The IUV diameter (*d*) was taken as the mean of five frozen images and the estimated fetal weight (EFW) was derived from measurements of the biparietal diameter and the abdominal trunk diameter (Eik-Nes *et al.* 1982*b*). Mean blood velocity ($\bar{v}$) in the aorta was calculated from the mean Δf_{max} over 10 cardiac cycles using the regression equation ($y = 0{\cdot}02567\,x - 2{\cdot}264$) and converted into volume flow (Q) by the equation:

$$\text{Equation 2.}\quad Q = \frac{\bar{v}\cdot\frac{\pi d^2}{4}}{EFW}$$

Measurements were taken when no whole body fetal movements were occurring. If fetal movements were present the mean Δf_{max} obtained from the umbilical vein was averaged over 5 s and volume flow calculated as in equation 2.

Results

In-vitro study

The standard deviations of the five pump flow stability tests ranged from 2·36 to 4·9 ml/min for flow rates of 110 and 610 ml/min respectively.

The graph of mean Δf_{max} against the true mean velocity as measured directly from the model system is shown in Fig. 2. The regression equation permits prediction of mean velocity from any given mean Δf_{max}. The standard error in velocity derived from this equation for a mean Δf_{max} of 500 Hz is 1·44 cm/s and for a mean Δf_{max} of 2000 Hz is 1·33 cm/s.

In-vivo study

In this longitudinal study of 15 women only five out of 92 potential observations were lost due to failure of the woman to attend (for non-obstetric reasons). Fetal movement, position and attitude could prevent good Doppler signals being obtained. Direct occipito-anterior positions increased the difficulty of visualizing and measuring the IUV and increased fetal flexion resulted in an insonation angle between the ultrasonic beam and the aorta greater than desired. Thus, out of 87 sessions, satisfactory signals were obtained from the IUV on 68 occassions (78%) and from the aorta on 71 occasions (82%).

Mean aortic diameter (SD) increased from 4·9 (0·6) mm at 28 weeks to 7·6 (1·1) mm at 40 weeks (Fig 3). The mean umbilical vein diameter (SD) increased from 6·0 (0·6) mm to

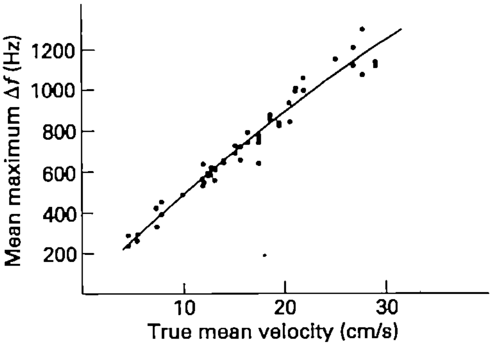

Fig. 2. Mean blood velocity through the phantom vessel in the model against the mean Δf_{max} obtained by the Doppler equipment

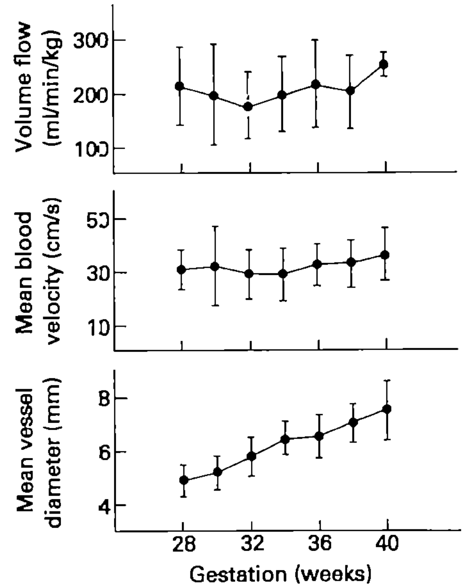

Fig. 3. Mean blood flow, mean blood velocity and mean vessel diameter of the descending aorta in normal fetuses

8·7 (0·5) mm (Fig. 4). Absolute volume flow remained constant in both the aorta and umbilical vein throughout gestation. Mean aortic flow for all women (n =71) was 206 ml/min/kg (SEM 8·5) (Fig. 3), and mean umbilical vein flow (n = 68) was 125 ml/min/kg (SEM 7·5) (Fig. 4). Mean velocity in both vessels was again constant irrespective of gestational age with a mean velocity in the aorta (Fig. 3) of 31·2 cm/s (SEM 1·13) and 12·8 cm/s (SEM 0·08) in the umbilical vein (Fig. 4).

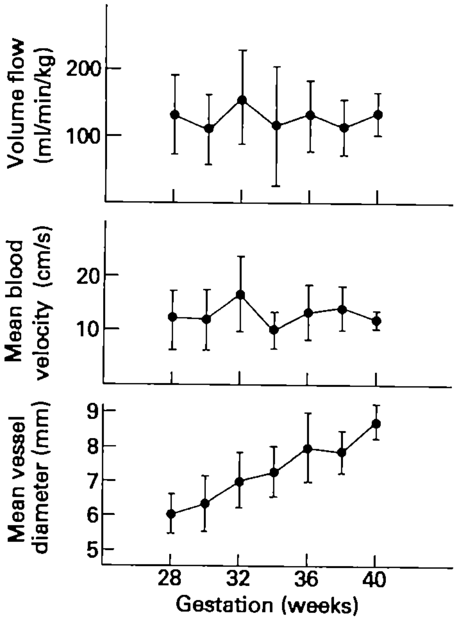

Fig. 4. Mean blood flow, mean blood velocity and mean vessel diameter of the intra-abdominal portion of the umbilical vein in normal fetuses

Discussion

There are several theoretical objections to the extrapolation of in-vitro results to in-vivo studies; nevertheless the preliminary calibration experiments using the ATL Mark V permitted results to be obtained with this equipment which compare favourably with those of other workers using a variety of techniques (see Tables 1 and 2). Eldridge (1981) also used the ATL Mark V, but reported only 22 measurements in a cross-sectional study and calculated flow from the mean output of the sample volume, which we believe, for reasons stated earlier, to be inaccurate.

Table 1. Previously reported results of aortic blood flow

Author	Aortic blood flow (ml/min/kg)		
	Mean	SEM	SD
Eik-Nes *et al* (1980)	191	12·2	62
Eldridge (1981)	166	6·0	28
Eik-Nes *et al* (1982*a*)	185	7·6	44
Griffin *et al* (1983)	246	3·5	30
Erskine & Ritchie (1985)	206	8·5	72

Table 2. Previously reported results of umbilical vein blood flow

Author	Umbilical vein blood flow (ml/min/kg)		
	Mean	SEM	SD
Gill & Kossoff (1979)	103	—	—
Eik-Nes *et al* (1980)	110	5·8	26
Gill *et al.* (1981)	90–120	—	—
Eik-Nes *et al.* (1982*a*)	115	6·9	36
Rajhvajn & Kurjak (1981)	109	—	—
Kurjak & Rajhvajn (1982)	107	—	—
Griffin *et al.* (1983)	122	3·1	21
Erskine & Ritchie (1985)	125	7·5	62

In this longitudinal investigation the flow rate in both the aorta and umbilical vein was found to be independent of gestational age, whereas Gill *et al.* (1981) found a slight fall after 35 weeks gestation. This difference might be explained by the fact that not only was their study cross-sectional but their estimation of fetal weight was based on extrapolation back from the subsequently known birthweight. Our objective was to assess the clinical potential of the technique, and therefore we used ultrasonically derived estimations of fetal weight.

Mean blood velocity in both vessels was also constant irrespective of gestational age, thus leaving only the steady increase in vessel diameter with gestation to account for the rise in total blood flow. The finding of constant mean blood velocity, together with the observation of Stuart *et al.* (1980) that the rate of acceleration of blood remains constant under normal conditions throughout pregnancy suggests that fetal cardiovascular haemodynamics remain remarkably stable throughout gestation.

The possibility that flow might be altered in the growth-retarded fetus is intriguing, but the Doppler techniques are at present prone to considerable errors. As can be seen in Tables 1 and 2, the results of mean flow in normal pregnancy in various studies lie within a narrow range, but most of these reports do not give any indication of the individual variation within the series, or only give the standard error. Where both the standard error and the number sampled have been reported we have calculated the standard deviation, which reveals that the error involved can range up to 35% for flow in the aorta and 35% to 50% in the umbilical vein. Such an order of error seriously limits the technique for clinical investigation, since changes in flow are unlikely to be of the order of 50% or greater except in extreme circumstances.

In increasing order of magnitude, these errors in estimating flow in terms of ml/min/kg lie in the primary acquisition and manipulation of the Doppler-shifted frequencies, the conversion of these frequencies to represent mean blood velocity using the angle of insonation and the estimation of both mean vessel diameter and fetal weight.

In our series there were a total of 87 scans performed out of a total of 92 potential scanning sessions, but satisfactory signals could only be obtained from the aorta in 71 cases (82%) and from the intra-abdominal portion of the umbilical vein in 68 cases (78%). Failure to obtain flow rates was due either to persistent marked whole-body fetal movements or to fetal positions which did not permit good visualization of the relevant vessels either for obtaining Doppler signals or for accurate diameter measurement. These difficulties further impaired the clinical usefulness of the technique. However, it must be conceded that some of the difficulty in obtaining signals occurred because a satisfactory angle between the Doppler signal and the vessel could not be achieved. This was in part due to the equipment we used, in which the Doppler signal originates from within the arc of the sector scan system. This problem may be reduced by using equipment with a linear array system in which the Doppler signal originates at an angle alongside (Griffin *et al.* 1983).

Doppler signals from the cord umbilical artery were also studied in the same group of patients, and reliable signals were obtained easily in all cases. We believe that qualitative analysis of the Doppler-shifted signals from this artery hold much more clinical potential than quantitative measurement of flow in the aorta or umbilical vein (Erskine & Ritchie 1985).

Acknowledgments

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Umbilical artery blood flow characteristics in normal and growth-retarded fetuses

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Summary. Time–velocity waveforms or sonograms obtained by pulsed Doppler ultrasound from the umbilical artery were analysed in a longitudinal study of 15 normal pregnancies. The sonograms from nine fetuses with intrauterine growth retardation were compared qualitatively and had quite different characteristics implying a high distal impedance to blood flow. Methods of analysis capable of differentiating between the normal and abnormal sonograms are described and discussed.

Since the introduction of Doppler ultrasound by Fitzgerald & Drumm (1977) to study the characteristics of blood flow in the human fetal umbilical artery, attention has been directed mainly towards the quantitative measurement of mean blood flow in other vessels such as the aorta (Eik-Nes *et al.* 1980, 1982; Eldridge 1981) and in the intra-abdominal portion of the umbilical vein (Gill & Kossoff 1979; Eik-Nes *et al.* 1980, 1982; Gill *et al.* 1981; Kurjak & Rajhvajn 1982). The clinical potential of such observations is limited not only because of the inherently large errors involved in the estimation of both vessel diameter and fetal weight, but also because of the significant rate (18% to 22%) of failure to obtain useful Doppler signals (Erskine & Ritchie 1985).

Such signals, however, can always be obtained reliably and quickly from the umbilical artery in the cord. In order to avoid the inherent inaccuracy involved in measuring blood flow we set out to examine the qualitative differences between umbilical artery sonograms in normal and growth-retarded fetuses, and to assess the methods by which these can be analysed.

Subjects and methods

A range-gated pulsed Doppler Mark V Duplex Ultrasonic Sector Scanner (Advanced Technology Laboratories) was used to visualize the umbilical artery within the umbilical cord. The sample volume was placed within the vessel using the range-gate facility on the line representing the Doppler beam superimposed on the real-time image. The Doppler mode was engaged, and by listening to the audio output the sample volume was placed to cover the lumenal centre of the vessel where maximum blood velocity occurs (McDonald 1974). When good quality Doppler-shifted frequencies (Δf) were obtained both by visual reference to the sonographic display of these frequencies and by their audio output, a hard copy printout of Δf was recorded after spectral analysis (Fig. 1). The sonograms were later subjected to secondary analysis.

Secondary sonogram analysis

The height or maximum Δf ($\Delta f_{\max}$) of the sonogram during a cardiac cycle is dependent on the angle of insonation between Doppler beam and blood vessel. This angle must be known accurately to compute absolute blood velocity from which mean blood flow can be calculated. Analysis of the variation in the $\Delta f_{\max}$ over the

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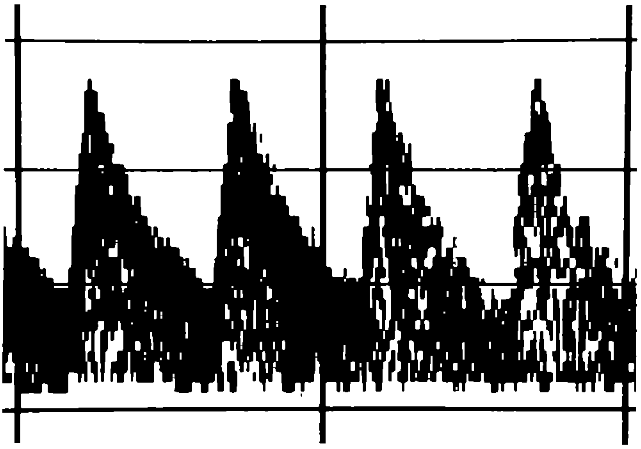

Fig. 1. Normal umbilical artery sonograms. blood velocity against time

cardiac cycle, however, has the advantage of being independent of this angle (Atkinson & Woodcock 1982) If a ratio of the maximum frequency during systole and diastole is calculated a dimensionless index independent of the insonation angle can be created, which mathematically characterizes the shape of the sonogram. This feature of angle independence is particularly useful in the umbilical artery as its sinuous path along the umbilical cord renders an accurate measurement of the beam angle very difficult. Several different dimensionless indices can be used to extract information contained within the sonograms about the qualitative nature of blood flow.

Gosling & King (1975) described the pulsatility index (PI) initially in terms of the Fourier transform harmonics, but subsequently simplified it to an equation where the height of Δf_{max} in systole minus the height of Δf_{max} in diastole on the sonogram is divided by the net mean height over the cardiac cycle (Fig. 2). This index has been shown to be sensitive to changes indicative of downstream impedance to flow (Skidmore *et al.* 1980).

The Pourcelot index (PoI) was created to study changes in impedance within the carotid artery (Atkinson & Woodcock 1982) and is obtained by dividing the difference between systolic and diastolic heights by the systolic height (Fig. 2). Fitzgerald & Drumm (1977) and Stuart *et al.* (1980) used the simpler ratio of maximum systolic height to end-diastolic height (A/B) in their study of umbilical artery sonograms in normal pregnancy (Fig. 2).

In the umbilical artery there is normally very low distal impedance to flow (Dawes 1968; Fitzgerald & Drumm 1977; Stuart *et al* 1980) and as a result there is forward flow in this vessel throughout the cardiac cycle. This contrasts with the adult femoral artery, for example, in which impedance is high, causing reverse flow to occur in diastole. In arteries with low impedance like the umbilical artery the end-diastolic velocity is inversely related to peripheral impedance (Olson & Cooke 1975) We therefore created an impedance index (ImI) designed to be more sensitive to small changes in the end-diastolic velocity This was achieved by dividing the product of mean Δf_{max} and systolic Δf_{max} by the square of the end-diastolic Δf_{max} (Fig. 2).

Five measurements (namely maximum systolic height, end-diastolic height, peak-to-peak distance, cardiac cycle length and area under the curve) were taken from each umbilical artery

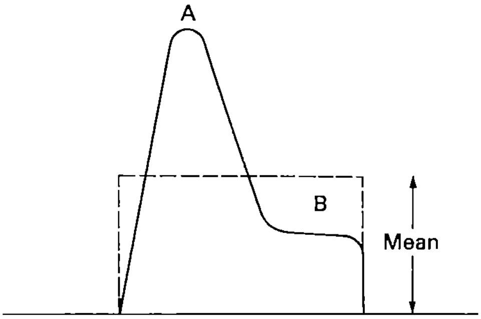

Fig. 2. Schematic umbilical artery sonogram with measurements required for secondary analysis and calculation of impedance indices

Table 1. Details of the nine growth-retarded fetuses with significantly elevated umbilical artery impedance as detected by the pulsatility index

Fetus no.	Intrauterine death	Scan to delivery interval (days)	Mode of delivery	Birthweight (g)	Gestation at delivery (weeks)	End-diastolic velocity	Concurrent maternal pathology
1	No	6	ECS	2025	35^{+0}	Reduced	Diabetes and hypertension
2	No	13	ECS	1160	33^{+6}	Reduced	Severe PE
3	No	13	ECS	1870	33^{+6}	Reduced	Severe PE
4	No	1	ECS	650	30^{+4}	Zero	Hypertension
5	Yes	8	ND	not known	24^{+4}	Zero	Hypertension
6	Yes	7	ND	1580	35^{+6}	Reduced	Renal transplant
7	No	1	ECS	1350	33^{+4}	Reduced	Hypertension
8	No	3	ECS	2240	37^{+1}	Reduced	Central placenta praevia
9	Yes	2	ECS	1755	36^{+1}	Reduced	Hypertension and twin pregnancy

ND, no data; ECS, elective caesarean section; PE, pre-eclampsia.

sonogram and the four indices described above were calculated. These indices (PI, PoI, A/B and ImI) were assessed for sensitivity to changes in umbilical artery impedance.

Cardiac cycle variation

To determine the number of sonograms required to minimize variation between each cardiac cycle 100 consecutive waveforms from the umbilical artery of a normal fetus at 38 weeks gestation were analysed for each of the four indices.

Patients

Fifteen normal fetuses were each scanned at 24 and 28 weeks gestation and thereafter at fortnightly intervals until delivery. In addition, eight of these fetuses were also scanned at 4-weekly intervals from 16 weeks gestation and one from 20 weeks gestation. All had fetal maturity confirmed by ultrasonic scanning at 16 weeks gestation and all were considered clinically normal.

Nine fetuses suspected clinically and confirmed on ultrasonic scanning to have asymmetrical intrauterine growth retardation (IUGR) were also studied. These included one twin pregnancy where both fetuses (nos 2 and 3) were growth retarded and another where the second twin was growth retarded and died *in utero* (no 9). Further details are shown in Table 1. Three of the nine fetuses in this group died *in utero* (nos 5, 6 and 9). The remaining six pregnancies were terminated electively by caesarean section and all but one (no. 8) were delivered before 37 weeks gestation. All fetal weights were below the 10th centile for gestational age (Gairdner & Pearson 1971).

The information obtained from this study was not made available to those responsible for the clinical management of each patient.

Results

The standard error (SEM) of the mean PI was calculated for 100 consecutive umbilical artery sonograms. The percentage error incurred as the number sampled (n) rose from 1 to 100 is shown in Table 2. When 10 waveforms were sampled this error was 2·7%. Similar graphs were constructed for all four indices and all showed acceptable error rates when 10 cardiac cycles were examined. Analysis of five waveforms would not greatly increase this error, but the analysis of a single waveform would not be acceptable (Table 2).

Table 2. Percentage error for each index of impedance as sampling number (n) of sonograms increases

	PI	A/B	PoI	ImI
$n = 1$	8·3	7·5	5·5	18·2
$n = 3$	4·8	4·3	3·2	10·5
$n = 5$	3·7	3·3	2·5	8·1
$n = 10$	2·7	2·4	1·8	5·8
$n = 20$	1·9	1·7	1·2	4·1

Normal fetuses

From a total of 124 potential scans 119 were performed in the 15 women with normal pregnancies, five women failing to attend on one occasion each for reasons unconnected with their pregnancy Good quality signals from the umbilical artery were quickly and easily obtained in all 119 scans

The mean values (±2 SD) for each index are plotted against gestational age in Figs 3 and 4. All four indices gradually decreased with advancing gestation, indicating that placental impedance steadily falls as pregnancy advances.

Growth-retarded fetuses

A total of 24 scans were performed on the nine growth-retarded fetuses. In the majority the volume of amniotic fluid was reduced and visualization of the umbilical cord was therefore more difficult. Nevertheless, good quality signals were obtained from all fetuses In each abnormal pregnancy up to 30 min was spent ensuring that the best trace possible was achieved, although with experience the general sonographic pattern was usually quite apparent from the first few sonograms obtained.

In two fetuses (nos 4 and 5) one of which died *in utero* (no. 5) end-diastolic flow was totally absent on each occasion, as shown in Fig. 5. In the remaining 20 tracings from the seven other fetuses studied, subsequent analysis confirmed that each index was greater than 2 SD above the mean for gestational age. In each case the

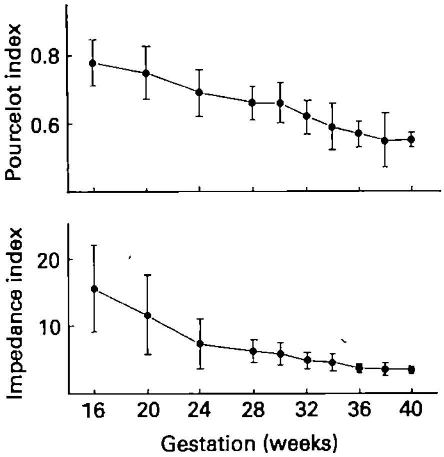

Fig. 3. Mean value (± 2 SD) for umbilical artery PI and A/B in normal pregnancies

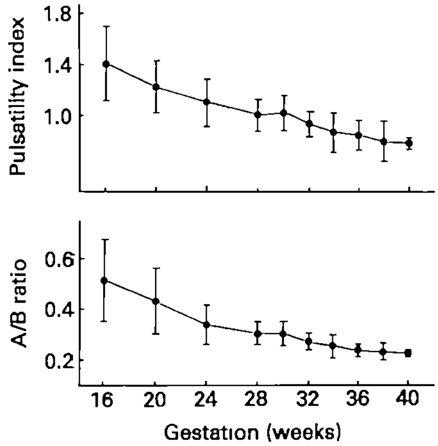

Fig. 4. Mean value (±2 SD) for umbilical artery PoI and ImI in normal pregnancies.

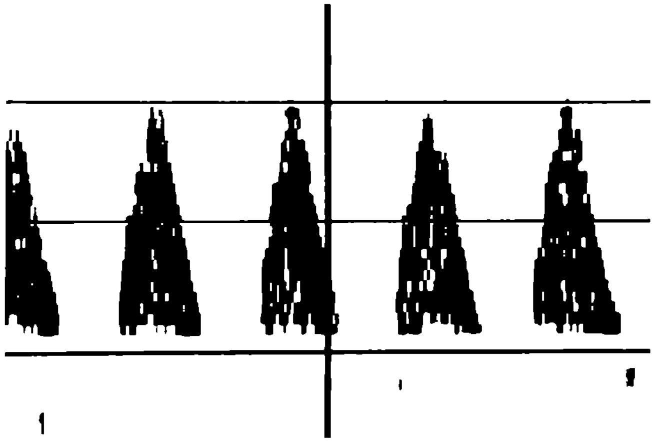

Fig. 5. Umbilical artery sonogram in a growth-retarded fetus (no. 4 at 29^{+6} weeks gestation) showing absent flow during diastole

decreased end-diastolic $\Delta f_{\max}$ was also quite obvious on visual inspection of the sonogram.

The normal range for PI (mean ±2 SD) derived from serial examination of the normal pregnancies described is shown in Fig. 6 for comparison with the PI values from each of the nine growth-retarded fetuses.

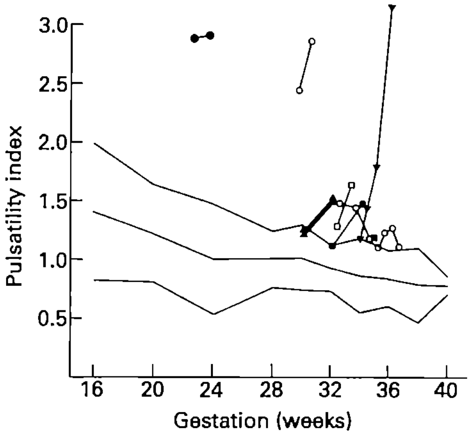

Fig. 6. Normal range of PI (mean ±2 SD) with PI values from nine growth-retarded fetuses (● no. 1; △ no. 2; ▲ no 3; ⊙ no. 4; ⊕ no 5, IUD; ■ no. 6, IUD; □ no. 7; ○ no. 8; ▼ no. 9, IUD).

Discussion

The advantage of the Doppler ultrasound technique described was the ease with which good quality signals from the umbilical artery could be obtained, often within 90 s of initiating the procedure, even in the presence of oligohydramnios. The only limiting factor was fetal movement causing the umbilical cord to change position, but recordings could be obtained between such movements since ≤10 s of fetal rest was sufficient to obtain good signals.

Fitzgerald & Drumm (1977) originally used a Doppler system which was unable to distinguish objectively between forward and reverse flow. The ability to discriminate between positive and negative Δf is of crucial importance, otherwise an apparent diastolic Δf arising from the umbilical artery can arise solely from superimposed non-pulsatile blood flow in the opposite direction in the simultaneously insonated umbilical vein. Stuart *et al.* (1980) modified the technique to obtain a directional facility but used continuous Doppler ultrasound rather than a pulsed system. This has the limitation that movement occurring anywhere along the beam can cause a Doppler shift in frequency which may be misinterpreted as arising from the umbilical artery. Similarly, if the placenta is sited on the anterior uterine wall low velocity signals from placental vessels could also be presented as diastolic umbilical artery flow. If the beam is pulsed, signals can be sampled from any site along the beam by use of the range-gate. This facility enables signals from the umbilical artery to be obtained even when the cord is lying close or posterior to the fetus, which often occurs with oligohydramnios.

Using four indices, all of which decreased, we have confirmed the original observation of Stuart *et al.* (1980) that there is an overall fall in umbilical artery impedance as normal pregnancy advances. The impedance index in particular demonstrates a large variation in end-diastolic $\Delta f_{\max}$ in the early second trimester which progressively lessens during the second and third trimesters, indicating that the fetoplacental circulation in normal late pregnancy is not only of very low impedance but is remarkably stable.

Preliminary studies suggest that the major change in the sonogram in the growth-retarded fetus occurs during diastole, indicating that blood flow during this period is substantially altered. It might be expected that the end-diastolic blood velocity would alter gradually, and consequently we created the impedance index in the hope of detecting early small changes. Three other established indices known to characterize blood flow were also used for comparison.

This study revealed that once an abnormal sonogram was obtained the change could be detected using any of the four indices. On four occasions the diastolic flow was zero, causing both the impedance index and the A/B ratio to become infinity. The Pourcelot index also rose to its maximum of unity. Only the pulsatility index could suitably quantify signals with zero diastolic flow. Furthermore, we have subsequently observed reverse diastolic flow in the umbilical artery and this again can only be handled adequately by the pulsatility index For these reasons this method is recommended for analysis of Doppler signals from the umbilical artery.

No fetus with normal umbilical artery resistance was growth retarded and no severely growth-retarded infant maintained a normal resistance. This technique appears to identify and confirm severe growth-retardation more accurately and quickly than any other present test. Three fetuses from our series of nine died *in* *utero* with very low or absent flow in diastole, which suggests that the technique may also identify those at serious risk of sudden intrauterine death.

The diagnosis of growth retardation in each of the fetuses investigated was suspected clinically and was confirmed by conventional ultrasonic measurements before flow studies were carried out. The umbilical artery impedance was already elevated by this time and could be demonstrated by each of the indices calculated. In some cases the PI increased rapidly as serial measurements were made. Further investigation is required to show how early these changes can be detected and whether or not the rate of change relates to fetal outcome.

The cause of this dramatic change is intriguing and demands further study. It may be due to an increase in placental bed resistance or to a change in the flow characteristics of blood in the cord. The latter may be due to altered viscosity which is known to be increased in growth retarded fetuses (Humbert *et al.* 1969; Mentzer 1978; Walker 1981).

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ST waveform changes of the fetal electrocardiogram during labour—a clinical study

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Summary. Waveform changes in the fetal electrocardiogram (ECG) are under reassessment as a means of fetal surveillance. The purpose of the study was to identify ST waveform changes from the fetal scalp lead during labour and to compare any change with conventional signs of fetal distress. Two scalp electrodes provided a sufficiently stable signal from which ST waveform changes could be identified and measured as the T/QRS ratio. No infant was clinically hypoxic. Only 26% of the 46 patients studied had a continuously normal CTG whereas 67% had no ST waveform abnormalities. A relation was found between the two variables as the mean T/QRS ratio increased from 0·20 (SD 0·11) during epochs of normal CTG to 0·27 (SD 0·17) with CTG changes. A linear correlation ($r=0{\cdot}58$, $P<0{\cdot}01$) was found between the T/QRS ratio before birth and the cord plasma lactate values.

Injury from birth hypoxia continues to be a major source of concern but there is also increasing concern about medical interference and maternal morbidity from unnecessary operative procedures.

Current methods of assessing intrapartum hypoxia by continuous fetal heart rate (FHR) monitoring and scalp blood pH measurements have failed to resolve the problem. Used alone, continuous FHR monitoring increases intervention with no measurable improvement in fetal outcome (Haverkamp *et al.* 1979). Fetal scalp blood sampling for pH should reduce unnecessary intervention but is only used in 40% of units in the UK (Gillmer & Combe 1979) and the validity of scalp capillary measurements as the head is compressed in the pelvis is again being questioned (O'Connor *et al.* 1979).

Since Cremer (1906) obtained the first fetal electrocardiogram (ECG) many workers have strived, without success, to establish a diagnostic place for changes in the fetal ECG waveform. There may be many reasons for this but one of the more important is that filters, used to obtain a satisfactory signal to noise ratio, distort the low frequency components of the ST waveform (Berson & Pipberger 1966; Greene 1983). Without them, low frequency noise may produce apparent changes in the ST waveform (Hon & Hesse 1960). It is this portion of the ECG which is most likely to change with metabolic disturbance.

In experiments in acutely exteriorized fetal lambs and guinea-pigs, hypoxia with acidaemia produces changes in the ST segment and T wave. The main response was progressive increase in T wave amplitude (Rosén & Kjellmer 1975) and this was also an independent finding of Pardi *et al.* (1971). These changes occur before signs of failing cardiovascular function (Rosén *et al.* 1976*a*) and contemporaneously with changes in the somatosensory-evoked EEG response (Rosén *et al.* 1976*b*). Changes are also correlated to the anaerobic breakdown of myocardial

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glycogen stores (Rosén & Isaksson 1976, Hökegård *et al.* 1981) and similar changes may be reproduced by beta-adrenoceptor stimulation (Hokegård *et al.* 1979). Recent observations (Greene *et al.* 1982) in the chronically instrumented fetal lamb confirm that ST waveform elevation occurs not with hypoxaemia *per se* but when that is sufficient to cause anaerobic myocardial metabolism In man Pardi *et al.* (1974) have demonstrated alterations in the fetal ST waveform in some cases with variable and late decelerations, and elevated T waves on the neonatal ECG at delivery are associated with previously abnormal FHR patterns (Hökegård *et al.* 1978).

In the lamb the fetal and neonatal ECG were obtained from chest leads and the use of fetal scalp leads alone presents new problems. There are difficulties in obtaining a noise-free signal and the different and distant relation of the electrodes to the fetal heart might obscure changes. Thus clinical development of ST waveform analysis for intrapartum monitoring would depend on: the demonstration of similar changes from these peripheral leads; evidence that changes provided additionally useful information; and the ability to quantify changes automatically and objectively. This study attempted to clarify the first two points.

Subjects and methods

Of the 46 patients in the study whose labours were monitored, 32 were nulliparous and 14 were parous. Before labour 23 were considered low-risk and 23 were considered high-risk on the basis of growth retardation (7), hypertensive states (14), gestational diabetes (1) and maternal drug addiction (1).

Labour was induced in 30 patients by amniotomy and oxytocin or intravaginal prostaglandin gel. Twenty patients had operative deliveries: emergency caesarean section in eight, forceps delivery in nine and vacuum extraction in three. The indications for operative delivery were clinical fetal distress (10), failure to progress (9) and uncontrolled blood pressure in labour (1). Fetal scalp pH measurements were made on four patients by the clinicians managing them. The mean birthweight was 3230g (range 2360–4480). Three infants were small-for-dates (>2 SD below the mean).

The fetal ECG was recorded from two scalp electrodes (one spiral and one Copeland electrode) (Surgicraft, Redditch, England and To Med AB, Göteborg, Sweden) 2–4 cm apart and a silver/silver chloride wire electrode wound around an intrauterine pressure catheter tip (Fig. 1). The ECG was usually recorded between the scalp electrodes with the catheter electrode as the indifferent electrode, but comparisons were also made with one of the scalp electrodes as indifferent. The signal was processed simultaneously through a Hewlett-Packard cardiotocograph 8030A for a standard cardiotocograph (CTG) recording, and through an Elema-Schonander cardioscope EMT 343, used as a pre-amplifier, linked to an Elema-Schonander 34 Mingograph recorder for examination and write out of the ECG waveform (Bandpass: 0·1–800 Hz). No additional filters were used.

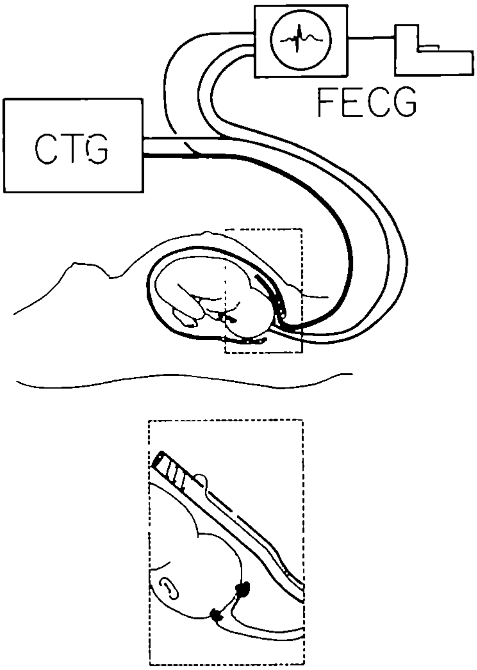

Fig. 1. Example of the recording technique used with two scalp electrodes and an intrauterine catheter electrode.

In four patients the ECG signal from the two scalp electrodes was compared with that from the usual single scalp electrode by simultaneous recording through two Elema-Schonander cardioscopes of matched gain. The indifferent pole for the two leads was the maternal thigh.

In all patients the fetal ECG waveform was monitored by an oscilloscope and intermittently recorded on paper for later comparison with the CTG. Thirty-minute epochs of the CTG, embracing an ECG recording, were classified without knowledge of the ECG waveform into normal, intermediate or abnormal groups according to the criteria detailed in Table 1. A single abnormal characteristic was sufficient to classify an epoch to the intermediate or abnormal groups. On the basis of results in the fetal lamb (Rosén *et al.* 1976*a*; Greene *et al.* 1982) the ST waveform of the ECG was judged abnormal, if the amplitude of the T wave exceeded that of the P wave. To enable quantitive comparison of T wave changes ruler measurements of the T wave and QRS complex were expressed as the T/QRS ratio, thereby correcting for changes in signal gain.

Table 1. Classification of intrapartum cardiotocogram (CTG)

Normal CTG
  Basal heart rate 120–160 beats/min
  Heart rate variability (band width) 10–25 beats/min
  No decelerations*

Intermediate CTG
  Basal heart rate 100–120 or 160–180 beats/min
  Heart rate variability (band width)>25 beats/min
  Heart rate variability (band width)<5–10 beats/min†
  Early decelerations in first stage
  Mild variable decelerations. >80 beats/min for <60 s duration

Abnormal CTG
  Basal heart rate <100 or> 180 beats/min
  Heart rate variability (band width)<5 beats/min in absence of sedation
  Moderate–severe variable decelerations: <80 beats/min for >60 s duration
  Late decelerations

*Early decelerations accepted as normal in second stage.
†Band width 5–10 beats/min accepted as normal together with accelerations.

All newborn infants were assessed by Apgar scores at 1 and 5 min and by paediatric assessment on the first day and before discharge home. Umbilical artery pH was measured in 10 patients and umbilical vein pH and lactate in 21 patients. Blood was collected in heparinized syringes stored on ice; pH measurements were made within 15 min of collection and blood for lactate measurement was deproteinized, centrifuged and the supernatant deep-frozen for later analysis by an enzymatic method (Biochema Test Combination, Boehringer-Mannheim).

The patients remained under the clinical care of obstetricians unconnected with the research project and decisions on management (including fetal scalp sampling) were made by them.

Student's *t*-test and linear correlations were used for statistical analysis.

Results

ST waveform assessment was possible from the unfiltered ECGs in all 46 patients though there were times when low-frequency shifts in the baseline prevented measurement. There was less baseline fluctuation with the scalp–scalp-catheter electrode configuration than with the usual scalp–vaginal electrode (Fig. 2) but T wave changes could be measured from the latter during stable conditions and these were not significantly different. Changing the indifferent electrode from catheter to scalp on the scalp–scalp-catheter electrode configuration recordings seemed to increase the signal amplitude but not alter the configuration. In the whole study the amplitude of the QRS complex varied between 200 and 300 μV. As Tables 2 and 3 show,

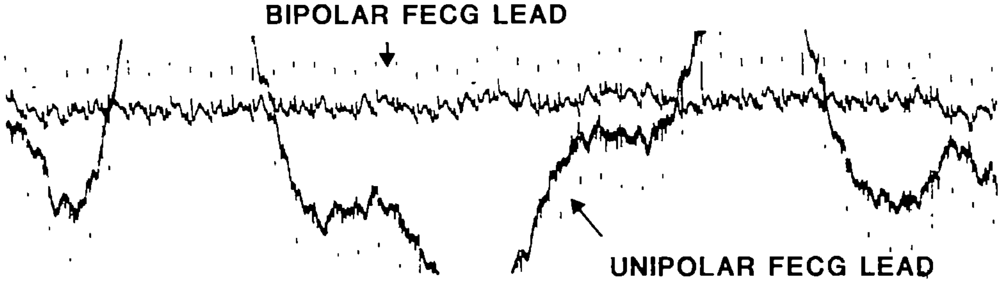

Fig. 2. Simultaneous fetal electrocardiograms (FECG) recorded either by using a single scalp electrode (unipolar) or two scalp electrodes (bipolar). The indifferent electrode was on the maternal thigh in each case

Table 2. Distribution of patients with or without an abnormal cardiotocogram (CTG) and fetal electrocardiogram (FECG)

	n	Normal CTG	Intermediate CTG	Abnormal CTG
Normal FECG	31	11	7	13
Abnormal FECG	15	1	0	14
Total	46	12	7	27

n=Number of simultaneous FECG and CTG recordings

the T wave amplitude is more usually less than, or equal to, the amplitude of the P wave.

Table 2 shows the distribution of CTG and ECG findings in the 46 monitored patients Only 12 (26%) had a continuously normal CTG whereas 31 (67%) had a continuously normal ST waveform with no increase in the T/QRS ratio as labour progressed. The ST waveform was normal when the CTG was classified as abnormal in 13 patients and intermediate in seven

ST waveform changes, with the T wave exceeding the P wave, occurred in 15 patients but in eight the T wave elevation was transient lasting <15 min. In all but one of these the CTG was either intermediate or abnormal over the same period Fig. 3 illustrates such an example. In the other seven patients the T wave was elevated for 30–130 min with considerable fluctuation in the T/QRS ratio with maximum values for each patient ranging between 0·32 and 1.12. These were all associated with an abnormal CTG classification. Fig. 4 illustrates the features in one patient with ST waveform changes through most of the labour. The patient, a primigravida with hypertension at term, was induced by intravaginal prostaglandin E_2 gel and developed uterine hypertonus with intrauterine pressures of 20–25 mmHg between contractions. The elevated T/QRS ratio varied between 0·57 and 1·12 with a noticeable increase with contractions and a decrease between contractions but also generally increasing as labour progressed. The CTG tracing showed mainly variable decelerations with periods of baseline bradycardia. The infant was born spontaneously with Apgar scores of 7 and 9 at 1 and 5 min respectively. The umbilical artery pH was 7·24 and the umbilical vein lactate value 5·15 mmol/1;

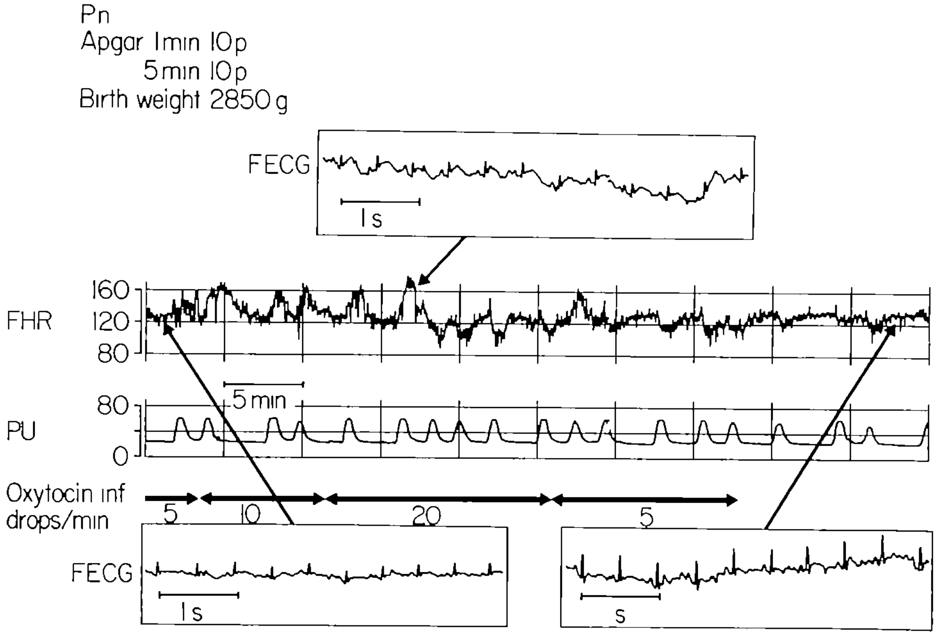

Fig. 3. Simultaneous recordings of the fetal electrocardiogram (FECG) and cardiotocogram during induced labour Temporary FECG changes were seen with an increase in the oxytocin infusion.

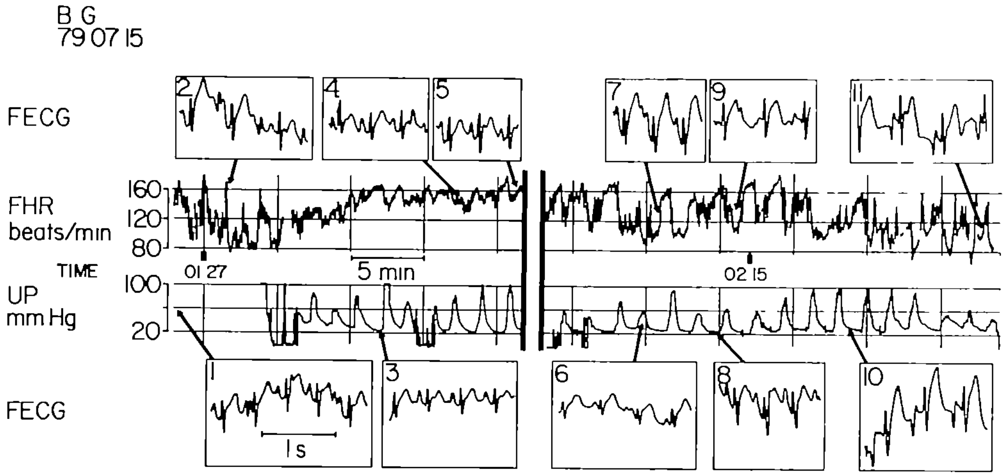

Fig. 4. Parallel recordings of the CTG and fetal electrocardiogram (FECG) during labour ST waveform changes are seen throughout the recording with variable decelerations and periods of bradycardia on the CTG

the neonatal period was uneventful.

In Table 3 the ST waveform was compared with the CTG classification in 126 epochs of 30 min from all patients, excluding one epoch with a negative T wave and normal CTG pattern. As stated, the ST waveform was considered abnormal if the T wave exceeded the P wave; the T/QRS ratio was significantly different ($P<0{\cdot}001$) if the ST waveform was normal (mean 0·20, SD 0·09) rather than abnormal (mean 0·42, SD 0·17).

A normal ST waveform occurred in 79% of epochs whilst a strictly normal CTG occurred in 37% of epochs. Abnormal ST waveforms occurred in 4% of CTG epochs classified as normal, 28% classified as intermediate and 33% classified as abnormal. There was a significant difference in the T/QRS ratio between the normal (0·20, SD 0·11) and intermediate (0·28, SD 0·13) CTG epochs ($P<0{\cdot}01$) and between the normal (0·20, SD 0·11) and abnormal (0·27, SD 0·17) CTG epochs ($P<0{\cdot}05$). Fetal scalp pH measurements obtained in four patients with an abnormal CTG pattern ranged from 7·35 to 7·38. The T/QRS was elevated in only one of those to 0·39.

ECG recordings were obtained within 30 min of delivery in 32 patients and in 21 of these umbilical vein blood was taken for lactate measurement. A linear correlation ($r=0{\cdot}58$, $P<0{\cdot}01$) was found between the T/QRS ratio of these recordings and the lactate values (Fig. 5). No correlation was found between the T/QRS ratio and umbilical cord pH measured in 23 of these patients (mean pH 7·31, range 7·20–7·45). No infant was clinically hypoxic as defined by an

Table 3. Electrocardiographic (ECG) changes related to cardiotocographic (CTG) findings—distribution of T/QRS ratios

ECG amplitude		CTG periods			
		Normal	Intermediate	Abnormal	Total
T<P	*n*	44	29	27	100
	T/QRS	0 19 (0·10)	0·23 (0·07)	0·20 (0·10)	
T<P	*n*	2	11	13	26
	T/QRS	0·43 (0·11)	0·42 (0 14)	0·41 (0·20)	
Total	*n*	46	40	40	126
	T/QRS	0·20 (0·11)	02·8 (0·13)**	0·27 (0·17)*	

Results are means (SD).
n=Number of simultaneous ECG and CTG recordings
*$P<0{\cdot}05$; **$P<0{\cdot}01$.

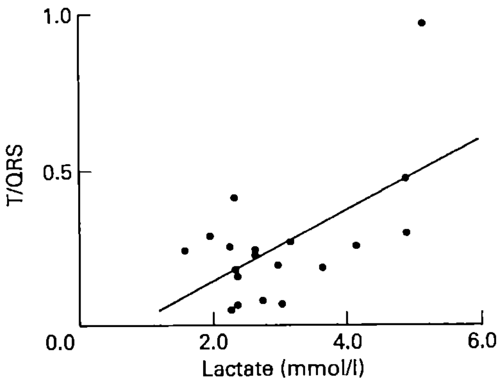

Fig. 5. The correlation between the T/QRS ratio recorded within 30 min of delivery and umbilical vein lactate values. $y=0{\cdot}115x-0{\cdot}102$; $r=0{\cdot}58$.

Apgar score of <7 at 5 min. The neonatal period was uneventful in all infants but one. This infant had a congenital atrioseptal defect with pulmonay artery stenosis and showed ST waveform changes throughout the second stage.

Discussion

In the present study and others with appropriate filter characteristics (Symonds 1971; Pardi *et al.* 1974; Hioki 1975; Marvell *et al.* 1980) the fetal scalp ECG has a T wave which is normally isoelectric or biphasic with a positive deflection no larger than the P wave. Only the study of Pardi *et al.* (1974) specifically examined the ST waveform and we have confirmed their findings of an elevated T wave in a proportion of cases with variable and late decelerations of the FHR. These changes can be identified on a conventional single scalp electrode but the use of two scalp electrodes improves baseline stability of the signal which reduces opportunities for ST waveform distortion. We now feel there is no particular advantage to the additional use of a catheter electrode.

The incidence of birth hypoxia was very low though half the patients were described as high-risk. Nevertheless, almost 75% displayed some fetal heart rate changes and in more than half (those classified as abnormal) these were worrying and might have justified scalp samples. This and the fact that one in five had an operative delivery for presumed fetal distress support the contention that FHR monitoring increases intervention without obviously improving results (Haverkamp *et al.* 1979). But ST waveform elevation occurred much less frequently and in all but one patient was associated with an 'abnormal' CTG. Changes were often short-lasting and in situations which were suggestive of temporary hypoxia and/or catecholamine output. It is well known that such episodes may occur in labour with recovery so that the infant shows no evidence of hypoxia at delivery.

Assessment of ST waveform elevation subjectively by the relative amplitudes of T to P waves could cause over-diagnosis of ST waveform abnormality since Marvell *et al.* (1980) have demonstrated that the P wave amplitude decreases by some 30% towards the end of normal labour. This emphasizes the importance of objective measurement by the T/QRS ratio.

Though ST waveform elevation occurs independently of heart rate change there is a significant correlation of an elevated T/QRS ratio with abnormal FHR patterns, as one might expect if both are related to hypoxia. There was also a correlation of the T/QRS ratio in the second stage with umbilical cord lactate levels but no such correlation existed with umbilical pH. Pardi *et al* (1974) similarily found no correlation of elevated T waves to scalp pH. This might be because none of our infants was acidaemic and lactate is a more sensitive index of cellular hypoxia (Low *et al.* 1981) and raised levels precede a pH fall by some hours during hypoxia in chronic fetal lambs (Greene *et al.* 1982).

In modern obstetric practice truly hypoxic infants are fortunately uncommon so there are practical difficulties in monitoring sufficient numbers to assess new indices of hypoxia. Though there was no overtly hypoxic infant the strength of this preliminary human study is that the data are entirely consistent with our findings in the fetal lamb. In these, hypoxia produces ST waveform elevation when there is activation of the sympathetic system with myocardial anaerobic glycogenolysis and lactate production (Greene *et al.* 1982; Rosén *et al.* 1984). We are encouraged that the T/QRS ratio can be measured from the fetal scalp ECG from which the continuous FHR is also measured. Thus two different variables are obtained without the need for additional transducers. If these preliminary results are confirmed by further studies, analysis of the ST waveform by measurement of the T/QRS ratio may help to interpret CTG changes more appropriately. We have not examined all the features of the ECG waveform and it is possible that some under investigation (Marvell *et al.* 1980) may prove additionally helpful.

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Fetal plasma renin and renin substrate in mid-trimester pregnancy

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Summary. Blood samples were obtained by fetoscopy from 30 fetuses in the middle trimester of pregnancy. The results indicate that high concentrations of renin and relatively low levels of renin substrate are present in the fetus early in pregnancy. These values are similar to those previously demonstrated in the full-term fetus.

The fetal renin–angiotensin system has been studied predominantly on cord blood samples from infants born in late pregnancy and these studies have shown high levels of renin with relatively low values of renin substrate (Vallotton *et al.* 1976).

Fetal renin concentration at elective caesarean section has been shown to be similar to maternal levels, and these values are substantially greater than those in normal non-pregnant women (Oparil *et al.* 1976). More recently no significant difference was shown between maternal venous, cord artery and cord vein renin or renin substrate concentration (Tetlow & Broughton Pipkin 1983) All previous studies have been performed on cord blood samples collected as an 'end stage' phenomenon at the conclusion of a pregnancy. During the course of fetoscopy in mid-trimester pregnancies performed for a variety of indications, the opportunity was taken to obtain fetal blood samples for the measurement of plasma renin (PRC) and renin substrate levels (PRS).

Patients and methods

Fetal blood samples were obtained from 30 fetuses at the time of fetoscopy. Samples were collected from the cord artery into EDTA and, after centrifugation, plasma samples were stored at −20°C for subsequent assay. Samples varied from 0·5 to 1 ml in volume and were assayed for plasma renin concentration by radioimmunoassay of generated angiotensin I (Craven & Symonds 1978) and for renin substrate by angiotensin I assay following the exhaustion of renin substrate by the addition of excess human renal renin (Warren 1980). Plasma renin activity was not measured because of the increased sample size required for this assay.

The indications for fetoscopy are shown in Table 1. The majority of patients were admitted for diagnosis of thalassaemia. The chromosomal abnormality exhibited a karyotype XXY and the two congenital abnormalities included one fetus with gastroschisis and one with multiple congenital abnormalities.

Results

The individual values for PRC are shown in Fig. 1, and the mean values are shown in Table 2. Comparable values for PRC in the cord artery blood from 10 normal fetuses obtained at vaginal delivery, and values obtained from 20 fetuses at elective caesarean section are also shown in the same table. It can be seen that the values are somewhat higher than those obtained at full term from infants delivered by elective cae-

Table 1. Indications for fetoscopy ·

Suspected thalassaemia	22
Normal fetuses	4
Fetal malformations	2
Chromosomal abnormalities	1
Duchesne's muscular dystrophy	1
Total	30

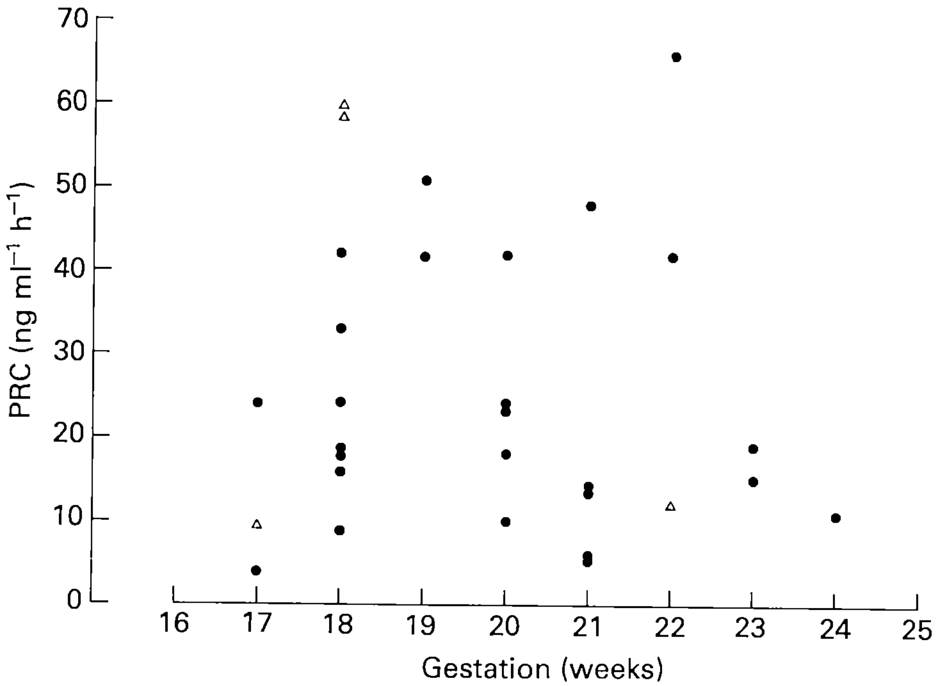

Fig. 1. Individual values for cord artery renin concentration (PRC) △ Normal fetuses

sarean section and lower than those obtained following vaginal delivery. Over the range of gestational age studied, there was no significant difference.

The values for renin substrate are shown in Fig. 2. The mean values for renin substrate are shown in Table 2 compared to similar substrate levels obtained at full term following vaginal delivery and elective caesarean section.

The values for PRC are higher than those described for maternal levels during pregnancy, and the renin substrate levels are less than maternal values.

Discussion

This study of PRC and PRS is unique in two respects. It is the first study in early human pregnancy; Franks & Hayashi (1979) measured plasma renin activity in three fetuses at 16–20 weeks gestation and showed that the levels were higher than maternal values obtained at the same time, but PRC and PRS levels were not measured in that study. Secondly, all previous reports related only to samples obtained following delivery either by abortion or vaginal or elective caesarean section, whereas this study was based on samples obtained from cord artery blood where the pregnancy was continuing. The results show that the levels of PRC are high in the fetus from early in pregnancy.

Samaras *et al.* (1982) showed levels of PRC were significantly higher in the fetus delivered vaginally in both normotensive and hypertensive primigravidae than in the mother and that cord

Table 2. Fetal plasma renin concentration (PRC) renin substrate (PRS) and gestational age

Weeks gestation	PRC (ng h^{-1} ml^{-1})	PRS (µg/ml)
16–18	26·4 (5·5)	1·8 (0·2)
19–21	25·0 (4·8)	1·7 (0·2)
22–24	27·5 (9·0)	1·8 (0·4)
Term (vaginal delivery)*	33·3 (7·0) (*n* = 10)	2·2 (0·3) (*n* = 8)
Term (elective CS)**	18·4 (2·1) (*n* = 20)	1·3 (0·1) (*n* = 20)

Results are mean (SD)
* Symonds *et al* (1984)
** Tetlow & Broughton Pipkin (1983)

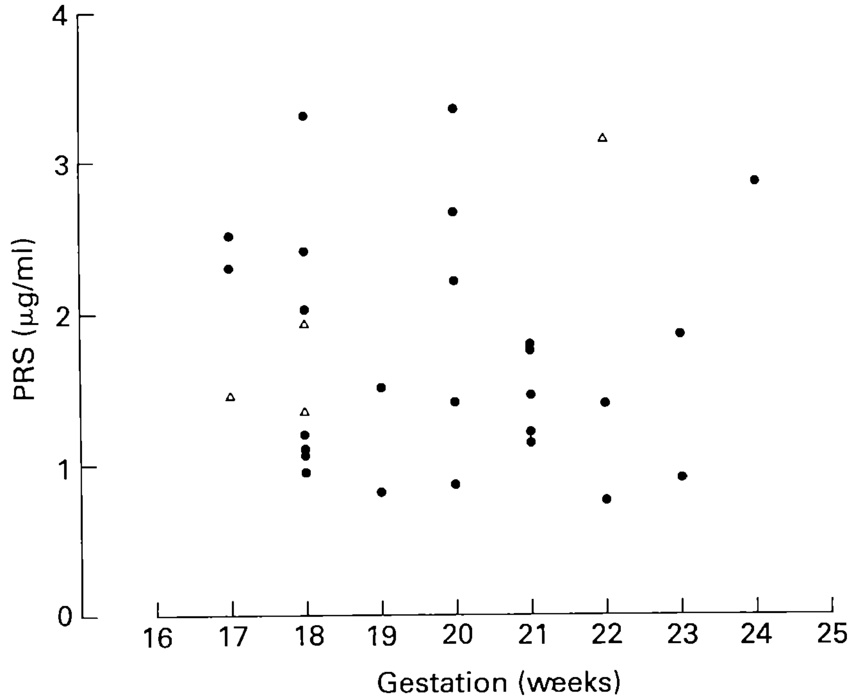

Fig. 2. Individual values for cord artery plasma renin substrate (PRS) levels. △ Normal fetuses.

artery and vein samples were similar. Vallotton *et al.* (1976) similarly showed elevated PRC levels in maternal and cord blood samples at vaginal delivery, with significantly higher levels in the cord; cord vein levels were higher than cord artery in six of the nine cases studied. They also found raised RS levels in the maternal blood compared to either cord vein or artery.

Symonds & Furler (1973) showed that renin substrate levels were approximately half those seen in the maternal circulation and the values obtained in the present study are similar. That study, on an anephric fetus, also suggested that the fetal renin–angiotensin system functioned independently from the mother, as very low levels of renin concentration were shown in its cord blood.

In this present study, it is apparent that the changes that occur in the fetal system in early pregnancy are similar to those seen in the full-term fetus.

Although the majority of samples were taken from fetuses with potential thalassaemia, those taken from four known normal fetuses fell within the same range and there is no evidence to suggest that the thalassaemia is associated with abnormalities of the RA system.

Acknowledgments

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Paediatric follow-up of pregnancies complicated by subnormal oestriol excretion

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Summary. A cohort of 1238 consecutive women seen early in pregnancy for accurate assessment of gestation had urinary excretion of oestriol measured at 30, 35 and 40 weeks; 92 had a low urinary oestriol excretion confirmed in hospital on at least one occasion. The women in the low-oestriol group were matched for racial origin and maternal age with 90 women in the study population who had persistently normal urinary oestriol excretion values (control group) and their infants were compared. Three infants born in the low-oestriol group and two in the control group subsequently died; 85 of the 89 (95·5%) survivors in the low-oestriol group and 84 of 88 (95·5%) control children were assessed by a paediatrician and a psychologist at the age of 6 years. Anthropometric measurements of children in the low-oestriol group at 6 years of age did not differ significantly from controls and their performance on most psychological tests was not significantly different. The subgroup of 25 children born to women with persistently low oestriol excretion during pregnancy showed a significant reduction in weight and head circumference at 6 years compared with the values in the control group and in the other children in the low-oestriol group. The children born to women with low oestriol excretion during pregnancy showed no increased evidence of developmental, neurological or physical defects at 6 years of age.

Measurement of maternal urinary oestriol in pregnancy is now accepted as a good index of fetoplacental function since low oestriol excretion is associated with an increased incidence of perinatal deaths, intrauterine growth retardation and malformations. The conclusions from early follow-up studies of infants born to mothers with low urinary oestriol excretion during pregnancy were contradictory; Wallace & Michie (1966), reported a high incidence of neurological and physicial defects in their small group of survivors, whereas Greene *et al.* (1969) reported a more favourable outcome. These divergent results may have been due to differences in the population sampled, and indicated the need for longitudinal prospective studies. This paper reports the results of such a study where follow-up was continued until all children reached the age of 6 years.

Patients and methods

For the years 1971 to 1973, 3858 standard ward patients who attended the Professorial Unit Clinic were delivered at the Royal Women's Hospital. The study population comprised the 1238 women who presented before 20 weeks gestation, had regular menstrual cycles, knew

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precisely the date of their last menstrual period and at the first antenatal visit the uterine enlargement was consistent with the period of amenorrhoea. These 1238 women collected 24-h urine specimens for measurement of oestriol excretion at 30, 35 and 40 weeks gestation; women with 'low oestriol excretion' and matched control women with normal oestriol excretion were available for follow-up assessment. Urine collections were made at other gestations only if ordered by the obstetrician, but otherwise patients were managed routinely in the clinic. Oestriol was determined by the method of Brown *et al.* (1968).

A subnormal 24-h urinary oestriol excretion was defined as any value below the straight line joining 8 mg at 30 weeks and 12 mg at 40 weeks or later (Wade *et al.* 1978). Those women with subnormal urinary oestriol excretion were admitted to hospital for a 24-h urine collection under supervised conditions; if this supervised oestriol excretion was subnormal, the woman was placed in the 'low oestriol series', irrespective of the subsequent pattern of oestriol excretion. Urinary oestriol excretion was then estimated at least weekly for the remainder of the pregnancy. Ninety-two infants of women with low oestriol excretion after 30 weeks of gestation were born alive and were subsequently followed up, these comprise the index group.

From the 1146 women with normal oestriol excretion we selected 90 who could be matched with each index patient for country of birth and maternal age within 5 years. Two patients with 'low oestriol excretion' born in Mauritius and Sri Lanka could not be matched for country of origin with control subjects. These 182 infants were included in the longitudinal follow-up study comprising 92 from women with low oestriol excretion and 90 from the control population. Of the 182 patients in the survey, 72 came from Australia or the British Isles, the remaining 110 coming mainly from Italy, Greece and Yugoslavia.

All 182 infants were examined by one of the authors (R.W.) shortly after birth and the anthropometric measurements, perinatal data and the presence of malformations were recorded and coded.

At each subsequent visit at 6 weeks, 1, 2, 3, 4 and 6 years of age, a clinical history and physical examination were performed and the Denver Developmental Screening Test (DDST) was used at all but the 6 year assessment (Frankenburg & Dodds 1957); the examiner was unaware of maternal urinary oestriol values and was not involved with the clinical care of the women or their infants in hospital.

Particular attention was paid to any factors which might have adversely affected development, such as the frequency of childhood illnesses, convulsions, accidents and hospitalizations. The timing of the establishment of laterality and occurrence of behaviour disorders were determined. If delivery had been preterm, the age at examination at all follow-up visits was corrected for prematurity. Centile measurements were coded to the nearest 10th centile using sex-specific charts appropriate for an Australian urban population (National Health and Medical Research Council of Australia 1975) to compare growth of the 'low oestriol' subjects and controls.

At the final comprehensive 6-year assessment screening tests of vision were made, using the 'E' chart, the acuity being recorded as abnormal if vision was less than 6/9 in either eye. The Stycar hearing test was used to assess the child's hearing, speech and to some extent, auditory memory (Sheridan 1975). If any abnormality was detected the patient was referred for more detailed assessment.

Psychological tests used at the 6-year assessment included the McCarthy Scale of Children's Abilities, the Bender Gestalt test, the Draw-A-Person test and scored the Bristol Social Adjustment Scale completed by the school teachers. In this report we selected the 'cognitive index' of the McCarthy Scale as a measure of the developmental outcome as it incorporates verbal, perceptual performance and quantitative aspects in its score and is directly referable to an IQ level; scores >85 were considered to be normal, 71–85 borderline and <71 abnormal. A score >9 on the Bender Gestalt test was considered abnormal (Koppitz 1963*a*). The Draw-A-Person was scored as described by Koppitz (1963*b*). The socioeconomic status of the families was recorded on the seven point Congalton Scale, based on the father's occupation (Congalton 1969).

Statistical analysis

All obstetric, neonatal and subsequent paediatric medical, social and psychological data were transferred to magnetic disc for computer analysis using Statistical Package for Social

Sciences (SPSS) programs (Nie *et al.* 1975). Differences in proportion were regarded as statistically significant in computer-produced tables if the corrected χ^2 (or Fisher's exact test for small numbers in 2×2 tables) indicated a P value $<0{\cdot}05$. Differences in distribution of psychological test scores were regarded as significant if two tailed t-tests gave a P value $<0{\cdot}05$. For growth centiles, non-parametric Mann–Whitney U tests were regarded as significant if the Z-values indicated a P value $<0{\cdot}5$.

Results

There were no significant differences between the 92 women with low oestriol excretion and the 90 control subjects in marital status, social class, maternal height, maternal weight, past obstetric history, antenatal complications in the present pregnancy, fetal distress in labour, mode of delivery or Apgar scores of <4 at 1 and 5 min.

Ninety-two women in the low oestriol group compared with the 90 women in the control group had a significantly higher incidence of rhesus isoimmunization (9 compared with 0, $P<0{\cdot}01$), antenatal radiological investigations (62 compared with 14, $P<0{\cdot}001$), surgical induction of labour (40 compared with 2, $P<0{\cdot}01$), endotracheal intubation and/or intravenous sodium bicarbonate administration at birth (31 compared with 14, $P<0{\cdot}01$), jaundice requiring phototherapy (6 compared with 0, $P<0{\cdot}05$) and birthweight below the 10th centile (14 compared with 3, $P<0{\cdot}02$).

There was a non-significant trend towards a higher incidence of hypoglycaemia, respiratory distress syndrome, neonatal seizures and apnoea in the low oestriol group. Full details were included in our preliminary report of the study (Wade *et al.* 1978).

Patterns of low oestriol excretion

Four distinct patterns of low oestriol excretion were seen in the 92 patients whose infants were followed up. (i) Group 1 ($n = 46$), oestriol excretion was initially low, but levels returned to normal without treatment and remained normal until delivery. (ii) Group 2 ($n = 9$), low oestriol values were interspersed with normal values, but the predominant pattern was low oestriol excretion. (iii) Group 3 ($n = 25$), all oestriol excretion values from 30 weeks gestation were low. (iv) Group 4 ($n = 12$), initial oestriol excretion at 30 weeks gestation was normal, but subsequent values fell to low levels.

None of the distinct patterns of low oestriol excretion was more common in women with pre-eclampsia, chronic renal disease, cardiac disease or rhesus D isoimmunization, however, premature delivery was more common in group 3 (all oestriol values low) ($P<0{\cdot}02$). Fetal distress was also more common in this subgroup of patients ($P<0{\cdot}05$), but the mean Apgar scores at 1 and 5 min were not significantly different from those in the other low oestriol categories or those in the control subjects. With the exception of infants in subgroup 4, the other 'low oestriol' infants weighed significantly less than control subjects. No significant differences between these groups were evident in any aspect of social data recorded.

In the low-oestriol cohort, three infants died and all three mothers had persistently low oestriol excretion during pregnancy. One baby had trisomy E karyotype and died at 2 days; the second infant, with diagnosed and treated congenital adrenal hypoplasia, died at 24 days from necrotizing enterocolitis; the third infant died at 15 months of age following an exchange transfusion for severe rhesus erythroblastosis, the baby developed necrotizing enterocolitis; most of the small bowel was resected; failure to thrive from malabsorption and poor socioeconomic conditions were responsible for the death. Two of the control infants also died during the follow-up programme, one as a result of a motor car accident and the other from leukaemia.

At the time of the final assessment at the age of 6 years, 85 of the 89 'low oestriol' infants who survived (95·5%) were assessed, as were 84 of the 88 (95·5%) surviving control infants. Five untraced children were presumed to be still in Australia; three children had returned to Italy, Greece and South America. Although these eight children were untraced at 6 years of age, three had been seen up to the 4-year assessment, three others had been seen at 2 years, one had been seen at 1 year of age and one had been seen only at the 6-week assessment.

Growth

The mean centiles for anthropometric measurements at birth and at each follow-up visit within the four low-oestriol groups and the control group are shown in Figs 1, 2 and 3. Infants born to women with low oestriol excretion weighed

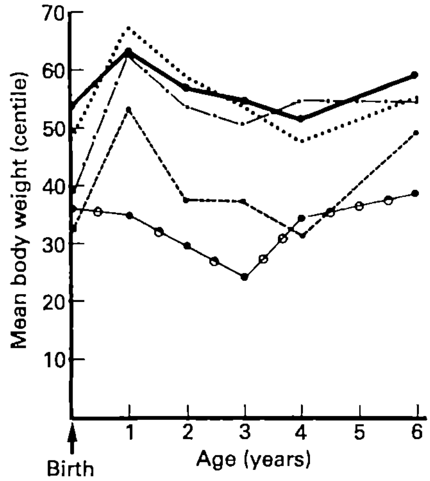

Fig. 1. Comparison of mean body weight centiles of control infants (———) with those born to women with low oestriol excretion (·—·—·—·) group 1; (– – – – –) group 2; (O–●–O) group 3; (··········) group 4.

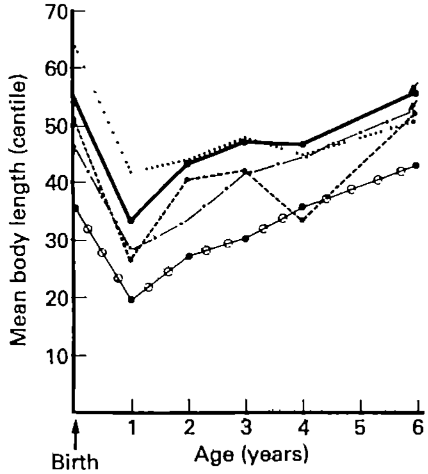

Fig. 2. Comparison of mean body length centiles of control infants with those born to women with low oestriol excretion. Symbols as for Fig. 1.

statistically significantly less at birth, and had a reduced head circumference and length (Table 1). Most of this significant difference was accounted for by the infants in the low-oestriol group 3 (persistently low oestriol excretion) and in this group alone the reduction in measurements persisted only to 4 years for height but to 6 years for weight ($Z = 1{\cdot}89$, $P<0{\cdot}05$) and head circumference ($Z = 2{\cdot}06$, $P<0{\cdot}05$). In three pregnancies placental sulphatase deficiency

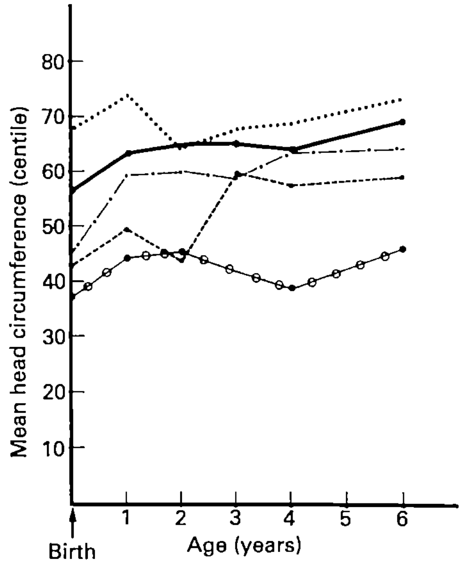

Fig. 3. Comparison of mean head circumference centiles of control infants with those born to women with low oestriol excretion. Symbols as for Fig. 1.

Table 1. Comparative analysis of growth measurements from birth to 6 years of age

Growth measurement	Control [centile mean (SEM)]	Low-oestriol [centile mean (SEM)]	*P**
Weight			
At birth	54·3 (2·8)	38·6 (2·6)	0·001
1 year	62·8 (3·1)	54·0 (3·7)	NS
2 years	57·0 (3·7)	45·6 (3·8)	0·05
3 years	55·5 (3·5)	42·8 (3·5)	0·04
4 years	51·7 (3·4)	46·2 (3·6)	NS
6 years	59·1 (3·2)	49·7 (3·6)	NS
Head circumference			
At birth	56·2 (2·7)	45·8 (2·8)	0·01
1 year	63·3 (3·2)	55·7 (3·2)	NS
2 years	64·4 (3·4)	54·7 (3·5)	0·05
3 years	64·9 (3·3)	55·5 (3·4)	NS
4 years	63·3 (3·4)	56·8 (3·5)	NS
6 years	68·7 (3·0)	59·4 (3·2)	NS
Length			
At birth	55·9 (2·7)	46·9 (2·6)	0·02
1 year	33·1 (3·1)	27·0 (2·9)	NS
2 years	43·4 (3·3)	33·8 (3·0)	0·05
3 years	47·7 (3·2)	39·3 (3·3)	NS
4 years	46·9 (3·3)	40·9 (3·4)	NS
6 years	55·8 (3·0)	49·4 (3·5)	NS

*Mann–Whitney test.

accounted for the persistently low oestriol excretion and the birthweights and subsequent growth of these infants were normal: this further increases the statistically significant growth retardation observed in the remainder of the infants in this low oestriol subgroup.

There were no significant differences in maternal weight or height between the control and the four low oestriol groups or, more particularly, between group 3 and the control group.

Sensorineural handicaps and psychological test results

The prevalence of the sensorineural handicaps in Table 2 showed no significant difference where children in the control group were compared with those in the entire low-oestriol group or only those born in group 3 (persistently low oestriol excretion). Children in the control and entire low-oestriol groups showed significant differences for only one of the battery of psychological tests, the General Cognitive Index of the McCarthy Scales; for individual subtests of the McCarthy Scale, the Bender/Gestalt and Draw-A-Man tests for the Bristol Adjustment Scale (Table 1) there were no significant differences.

Discussion

The increased concern on the part of the obstetrician and the consequent presence of a paediatrician at the delivery may explain the increased incidence in the low-oestriol group of premature delivery, radiological examinations performed, surgical induction of labour and neonatal resuscitation. Neonatal jaundice requiring phototherapy was the only neonatal complication which occurred more commonly in infants in the low-oestriol group, probably related to iatrogenic prematurity. Hypoglycaemia, which tended to occur more commonly in the low-oestriol group than in the control group, did not appear to be detrimental; prompt detection and

Table 2. Comparative analysis of sensorineural handicaps and psychological test results for low oestriol and control groups at 6 years of age*

	Control group	All low-oestriol subjects*	Group 3 low-oestriol subjects*
Sensorineural handicaps	(n = 84)	(n = 85)	(n = 22)
Cerebral palsy	1	1	1
Mentally retarded	3	3	2
Visual disturbances			
Strabismus	8	4	1
Acuity <6/9	8	10	3
Hearing deficiency†	7	11	2
Speech and language delay†	26	21	6
Behavioural disorders	10	10	4
Psychological tests	(n = 81)	(n = 83)	(n = 22)
General Cognitive Index			
Mean (SD)	92·2 (16·3)	86·9 (16·7)	84·4 (15·0)
Normal (>85)	50	46	10
Borderline (71–85)	22	23	8
Retarded (≤70)	9	14	4
Bender Gestalt			
Abnormal (score >9)	11	16	6
Draw-A-Person			
Abnormal	48	47	12

*Statistical analyses: the distribution for the General Cognitive Index for the control group was significantly higher than for the group of all low oestriol subjects (t = 2·03, P = 0·044) No other statistically significant differences were present in this table.

†Detected by Stycar hearing test

treatment may have averted sequelae. Pildes *et al.* (1974) also found no significant difference in mean IQ between infants with neonatal hypoglycaemia and their controls.

Our study indicated the need for control infants from the same hospital population when assessing growth. The control group had mean body weight and head circumference centiles higher at all assessment ages than the normal values reported at birth by Kitchen (1968*a, b*). Compared with the accepted Australian standard (National Health and Medical Research Council of Australia 1973) the children in the control group tended to be taller at 6 years. Infants born to mothers with low oestriol excretion were significantly smaller than the control infants at birth in all three growth measurements. Reduced uteroplacental function could reasonably be implicated in the growth retardation observed at birth. We speculate that reduced growth up to 6 years of age in children born to women with persistently low oestriol excretion may be due to intrauterine reduction in cell numbers. As all infants in the low-oestriol group were adequately matched with control subjects, it would seem unlikely that dietary deficiency after birth in this one specific subgroup would be the explanation.

Even if the two infants with cytomegalovirus infection, both with severe clinical manifestations of this disease, are included, there was no significant difference in the incidence of any neurological disabilities in the low-oestriol or control subjects. Even strabismus, often regarded as one of the mildest neurological problems, was not seen more often in the low oestriol group, or even in any of the low oestriol subgroups. This finding is at variance with that of other studies of infants from pregnancies associated with low oestriol excretion (Wallace & Michie 1966; Green *et al.* 1969; Butler *et al.* 1971). In these studies the incidence of strabismus was considered to be higher than that in the normal population, which was quoted as between 1 and 3%.In the current study the incidence of strabismus in the control group was 9·3% and it is possible the other workers recorded an incidence of strabismus in the normal population at too low a level which resulted in incorrect conclusions.

This study indicates that in pregnancies associated with low oestriol excretion and intrauterine growth retardation during the third trimester, the live born infants, if free of major malformations, usually develop normally, provided that perinatal care is of a high standard and the children receive appropriate care and environmental stimulation in the home. Paediatricians should also be aware that a normal physical growth pattern can usually be expected in such infants, with the exception of those children whose mothers had persistently low oestriol excretion during pregnancy.

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A pilot study of the frequency and significance of placental villitis

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Summary. The prevalence of inflammatory villous lesions was determined in a prospective study of 120 consecutive placentas. Cord blood IgM level was measured as an indicator of fetal intrauterine infection, and the birthweights of the infants were noted. Ten cases of villitis were found. Two infants had elevated cord blood IgM and one of them also had amniotic infection. As only one case of villitis had corroborative evidence of transplacental intrauterine infection, 90% of the lesions require an alternative explanation. The severity of the lesions correlated with the presence of low birthweight. The quality of the inflammatory infiltrate was also considered. Only one case included plasma cells; the remainder showed lymphohistiocytic infiltration. The case with plasmacytic infiltration was the one with elevated cord blood IgM. It is concluded that placental villitis is usually not an infective condition and its aetiology remains unknown.

Placental villitis is a lesion which has been associated with transplacental infection of the fetus, especially with viruses (Blanc 1978; Fox 1978; Blanc 1981). A subdivision of this lesion has been designated villitis of unknown aetiology (VUE) and is becoming increasingly recognized with an incidence varying from under 3% to 68% (Altshuler & McAdams 1972; Altshuler & Russell 1975; Altshuler *et al.* 1975; Russell 1980; Labarrere *et al.* 1982). It has been suggested that VUE is the larger category of placental villous inflammation (Russell 1980; Labarrere *et al.* 1982) in reports from a number of centres. The importance of VUE lies in its association with fetal intrauterine growth-retardation and perinatal mortality (Altshuler 1973; Altshuler & Russell 1975; Russell 1979; Russell 1980) and recurrent abortions (Russell *et al.* 1979; Russell 1980). Our observation of placental villitis in association with cases of unexplained stillbirth with negative viral culture and negative serology studies prompted us to perform a prospective pilot study of placentas to assess (i) the frequency of the lesion in our hospital populations, (ii) the clinical significance of the lesion and (iii) the role of infection.

Materials and methods

Placentas

A total of 120 consecutive, singleton placentas was collected without reference to the clinical details, from vaginal and caesarean section deliveries. The placentas were examined in the routine laboratory. They were weighed after trimming off the membranes and umbilical cord and random full thickness blocks of placenta were fixed in Bouins fluid, paraffin-embedded, and stained with the routine haematoxylin and eosin method. A minimum of two blocks of placental tissue were examined from each placenta (Russell 1980). Three blocks of umbilical cord and one roll of membranes were also processed

Pathological assessment

The sections were studied for evidence of inflammation of the cord, extraplacental membranes and chorionic villi. Villous inflammation was graded into mild, moderate and severe lesions as described by Russell (1980). Lesions were designated as mild when only occasional lesions were seen in any full thickness placental section and as moderate when they consisted of frequent focal infiltrates but where less than 25% of the placental tissue was involved. Severe lesions consisted of extensive diffuse placental villous inflammation with over 25% of the placenta affected. Viral inclusion bodies were carefully sought in all cases with inflammation of the chorionic villi. The quality of the villous inflammatory infiltrate was recorded as lymphocytic, histiocytic, plasmacytic or mixed. Acute inflammation of the extraplacental membranes (chorionitis) and/or umbilical cord (funisitis) were taken as markers of amniotic infection. If associated fetal pneumonic or gastric inflammation were noted, this was designated amniotic infection syndrome. Bacterial cultures were not always included.

Biochemical assessment

Prior to trimming the placenta, a specimen of cord blood was obtained by milking the cord. Each specimen of cord blood was code-numbered (V1–120) prior to IgM measurement.

The cord blood IgM levels were measured according to the sandwich enzyme-linked immunosorbent assay of Smeeth *et al.* (1983). The assay was performed by binding antibodies against human IgM to a microtitration plate. The addition of standard or test sera resulted in IgM of these samples becoming bound to the immobilized antibodies. A second antibody to the human IgM, which had been conjugated to the enzyme horse-radish peroxidase, was added and in turn became bound to the immobilized complex. The addition of the enzyme substrate resulted in colour development which was proportional to the concentration of IgM in the cord blood samples. The precision of the IgM method was determined using four pools of human sera containing different concentrations of IgM.

The reference range for IgM in cord blood was 0–450 mg/l and its distribution is illustrated in Fig. 1. It was determined by assaying 139 samples of cord blood from normal infants delivered between 36 and 40 weeks gestation.

Clinical details

Clinical details, gestational age, sex and birthweight of the infants, were subsequently collected on all cases of villitis. Birthweight-for-gestation charts of the Scottish Perinatal Mortality Review (1975–1979) were used for determination of centile weights.

Clinicopathological correlation

At the completion of the study, flow-charts were constructed showing, in tabular form, the case code-number, presence or absence of villous inflammation, presence or absence of cord–membrane inflammation, quality of the villous inflammatory infiltrate, and cord blood IgM levels (Table 1). Subsequently, the infant birthweights were compared with the grade of severity in cases of villous inflammation.

Results

Cases with abnormal findings are detailed in Table 1. In the 120 cases studied 10 examples of villitis were found. No gross abnormalities were found in any of these placentas. Nine of these cases revealed a lymphohistiocytic infiltrate and the tenth was the only example with plasma cells in the infiltrate. Two of the villitis cases were associated with raised cord blood IgM levels, but one also had evidence of amniotic infection to explain the fetal hyperglobinaemia, leaving only one case of villitis with a clear association with fetal infection. This one case is the only one with a plasma cell component in the lesion. Thus, eight of the 10 cases of placental villitis had no evidence of fetal infection and one had coexistent amniotic infection and villitis, so that 90%

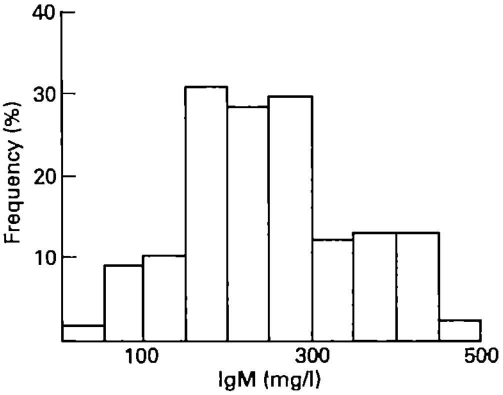

Fig. 1. Distribution of IgM in 139 normal cord bloods.

Table 1. Pathological and biochemical findings

Patient	Villitis	Amniotic infection	Cord blood IgM (mg/l)
V2	–	+	N
V8	+(LH)	–	N
V11	–	–	E (550)
V15	–	–	E (525)
V18	–	+	N
V20	+ (LH)	–	INS
V24	–	–	E (505)
V30	–	–	E (460)
V31	–	+	N
V34	–	+	N
V35	–	+	E (455)
V36	+ (LH)	–	N
V40	–	+	N
V41	–	+	N
V44	–	+	N
V50	+ (LH)	–	N
V51	–	+	N
V52	+ (LH)	–	N
V53	–	+	N
V58	–	+	N
V61	–	+	N
V67	–	+	N
V74	–	+	E (640)
V76	+ (LH)	+	E (610)
V77	–	+	N
V78	–	+	N
V80	–	+ (AIS)	N
V86	–	+	N
V89	–	+	N
V90	+ (LH)	+	N
V93	–	+	N
V94	–	–	E (580)
V95	–	–	E (500)
V97	–	+	E (610)
V98	+ (LP)	–	E (465)
V100	+ (LH)	–	N
V101	–	+	N
V108	–	+	N
V109	–	+	E (820)
V110	–	+	N
V112	–	+	N
V113	+ (LH)	–	N
V114	–	+	N
V115	–	+	E (730)
V118	–	+	N

+, Present; –, absent; L, lymphocytes; H, histiocytes; P, plasma cells; AIS, frank amniotic infection syndrome with intrauterine pneumonia; N, normal; INS, insufficient serum; E, elevated.

would merit the designation villitis of unknown aetiology (VUE). Viral inclusions were not noted in any of the cases.

The validity of cord blood IgM elevation as an indicator of fetal infection is supported by its association with acute inflammation of the membranes and cord, indicators of amniotic infection (Table 1). The cases of amniotic infection with normal cord blood IgM levels were all mild, early examples and were probably of too recent onset to have spread to the fetus.

Raised cord blood IgM levels were found in 13 cases. Seven of these had evidence of villous inflammation or amniotic infection. The remaining six had no such pathology, and the reason for the IgM elevation is not evident. The clinical correlation in the cases of villitis revealed a birthweight below the 10th centile in six of the 10 cases (60%). Five of these six cases (83%) had moderately severe villous lesions. Only one case of mild villitis was included and this accounted for the sixth case of low birthweight. This compares with the annual hospital rate of low-birthweight infants (birthweight below 10th centile) of 10%. The majority of the low-birthweight infants were associated with moderately severe placental villitis. There were no severe cases. There were no fetal deaths among the villitis cases. Of the remaining four cases of villitis with normal birthweights, three were moderate and one was mild. Other causes of low birthweight were considered. Case V20 (Table 1) had bilateral cystic renal dysplasia with normal female karyotype. Case V36 (Table 1) had maternal hypertension at term but the placenta showed no evidence of ischaemia, infarction or maternal vasculopathy. Only one infant had a birthweight below the 5th centile (Case V100) and its placenta showed moderate villitis.

Discussion

Placental villous inflammation is a well-recognized feature of transplacental fetal infection, especially with viruses, and the morphological characteristics of several of these viral placental infections are well established (Blanc 1978; Fox 1978; Blanc 1981). Recent studies have suggested that placental villitis in many, if not most instances may not be infective in nature (Russell 1980; Labarrere *et al.* 1982). That the lesion is important has been demonstrated by its association with fetal illness (Altshuler & Russell 1975; Altshuler *et al.*, 1975; Russell 1979, 1980; Labarrere *et al.* 1982), and the degree of fetal growth retardation has been shown to correlate with the severity of the villitis (Russell 1980). We, like others (Russell 1979; Blanc 1981), have recently noted the occurrence of placental villitis in cases of unexplained stillbirth and low birthweight with negative viral cultures and negative serology results. To investigate this situation, we sought to establish the frequency of villitis in our hospital population and to study its relation to other markers of fetal infection.

Our findings are almost identical with those of others (Altshuler & Russell 1975; Russell 1979; Russell 1980), with an overall incidence of the lesion of 8·3% and a strong correlation between the presence and severity of the lesion and low birthweight. A relation between villitis and congenital malformation is supported by Case V20 (Russell 1979).

The quality of the cellular infiltrate in placental villitis is also very similar to that described by Russell (1980). Most (90%) of the cases showed variable lymphohistiocytic infiltration and these represent all the VUE cases. Only one case had plasma cells in the lesion, and this case also had evidence of intrauterine fetal infection, with a raised cord blood level of IgM. This latter feature suggests, as others have indicated (Altshuler 1974; Blanc 1978; Blanc 1981), that the presence of plasma cells is a good indicator of an infective aetiology in placental villitis, and their absence warrants the designation VUE (Altshuler & McAdams 1972; Altshuler 1973; Russell 1980; Blanc 1981). The incidence of VUE appears to be similar in various populations (Altshuler & McAdams 1972; Altshuler & Russell 1975; Altshuler *et al.* 1975; Russell 1979, 1980; Blanc 1981) and may, therefore, represent a fundamental physiological aberration with a pathogenetic mechanism common to different populations.

The aetiology of this lesion requires further investigation. Although the cause is quite unknown, it has been suggested that failure of immune tolerance in pregnancy may be of importance in the pathogenesis (Blanc 1981; Labarrere 1982) as has been suggested for pre-eclampsia (Fox 1978; Labarrere *et al.* 1982) and recurrent abortion (*Lancet* 1983). It is tempting to speculate that VUE may lie in the middle ground of a gradient of such immune intolerance. This possibility is currently under investigation in this laboratory.

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Involvement of the vulval skin appendages by intraepithelial neoplasia

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Summary. In the treatment of vulval intraepithelial neoplasia (VIN) by laser, the extent to which the skin appendages are involved is an important factor in determining the depth of tissue to be destroyed. An investigation of 50 patients with VIN revealed that in 28 the skin appendages were involved and the maximum depth of involvement reached 4·6 mm from the surface of the epidermis. It is suggested that eradication of tissues to a depth of 5·0 mm would eliminate all atypical epithelium in the skin appendages.

A histological spectrum of vulval intraepithelial neoplasia (VIN) has been described (Buckley *et al.* 1983) and an increasingly large proportion of such lesions have been reported in women in their twenties (Forney *et al* 1977, Hilliard *et al.* 1979, Buscema *et al* 1980; Friedrich *et al.* 1980; Friedrich 1981; Benedet & Murphy 1982; Caglar *et al.* 1982; Bernstein *et al* 1983).

The management of VIN has changed in recent years as it was realized that the invasive potential of many of these lesions may not be great (Buscema *et al.* 1980; Friedrich *et al.* 1980) and radical surgical procedures are not required for their eradication (Jordan 1984). Indeed, they are undesirable because vulvectomy is disfiguring and an emotionally traumatic experience for many women Simple vulvectomy, topical chemotherapy with 5-fluorouracil and cryotherapy all have their proponents but have varying disadvantages (Rutledge & Sinclair 1968; Forney *et al.* 1977)

The carbon dioxide laser is a valuable tool for the treatment of a variety of intraepithelial neoplasms and under colposcopic guidance, it is possible precisely to control the extent of tissue destruction and the depth of penetration (Townsend *et al.* 1982). However, VIN may extend into the skin appendages and destruction of only the surface epithelium may therefore result in residual abnormal epithelium. Hence the extent to which the skin appendages are affected by VIN is an important factor when determining the depth of tissue to be destroyed. The magnitude of this problem has been investigated by determining the extent to which VIN may affect the skin appendages.

Subjects and methods

We examined 274 sections of tissue from 50 patients with VIN on file at St Mary's Hospital, Manchester. They included examples of VIN with and without dystrophy, VIN associated with single-cell invasive breaches of the basement membrane (Fig. 1) and VIN associated with invasive carcinoma measuring no more than 3 mm from the basement membrane of the epithelium from which it developed (stage 1A carcinoma). Tissue came from the labia majora, labia minora and the fourchette, but as it was not always possible to be certain of the precise source of the sample particularly in those patients undergoing repeat resections, the biopsy site has not been considered in the analysis of the data.

Measurements were made from haematoxylin and eosin stained 5-μm paraffin-processed sections using a linear measuring graticule in the eye-piece of the microscope and the ×4 objec-

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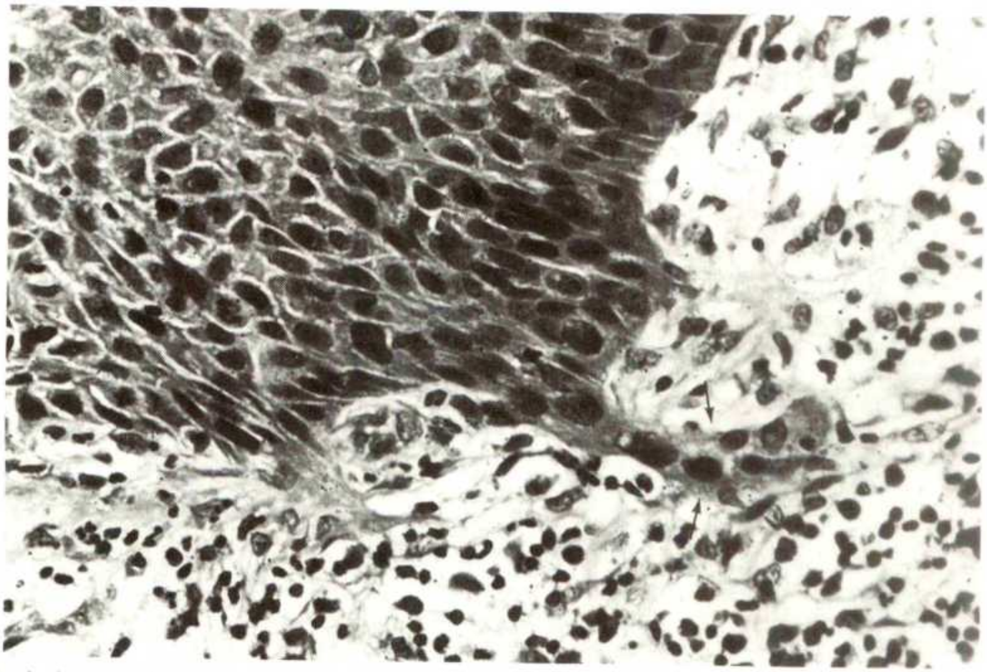

Fig. 1. An example of the early non-confluent stromal invasion (arrowed) referred to as single-cell invasive breaches of the basement membrane. H&E ×430.

tive. The histological characteristics were of necessity checked at higher powers of magnification.

The depths of the involved and uninvolved skin appendages, that is hair follicles, sebaceous glands and sweat glands, were measured perpendicularly from the epidermal surface to the base of the appendage and to the lower limit of the intraepithelial lesion. These slide measurements were regarded as a reliable indicator of the unfixed state, as it has been shown, in a similar study of cervical intraepithelial neoplasia (Anderson & Hartley 1980), that the fixed tissue dimensions differed from those of the fresh tissue by <5%.

Results

The characteristics of the lesions in 50 patients are shown in Table 1. In 27 there were histological features which suggested papilloma virus infection, that is koilocytosis, individual cell keratinization and multinucleation. The intraepithelial neoplasia extended into the skin appendages in 28 of the 50 patients (Fig. 2).

The majority of the lesions in which the skin appendages were affected had the features of VIN III (Table 2) and approximately the same proportion of these (15/28) had warty features as did the series as a whole.

The skin appendages reached a maximum depth of 9·7 mm and VIN involved the appendages to a depth of between 0·25 and 4·6 mm (mean 1·2 mm). Abnormalities were almost entirely limited to the hair follicles and sebaceous gland ducts and were most common in the hair follicles. In only one patient did VIN appear to affect a sweat gland duct (Fig. 3).

In all four patients with stromal invasion, even of a most minor degree, the depth of appendicular involvement was greater than average (Table 3).

Table 1. Characteristics of vulval intraepithelial neoplasia (VIN) in 50 patients

Lesion	Number of patients
VIN with hyperplastic dystrophy	33
VIN with mixed dystrophy	4
VIN without dystrophy	8
VIN with single cell invasion	3
VIN with small carcinoma	2
Total	50

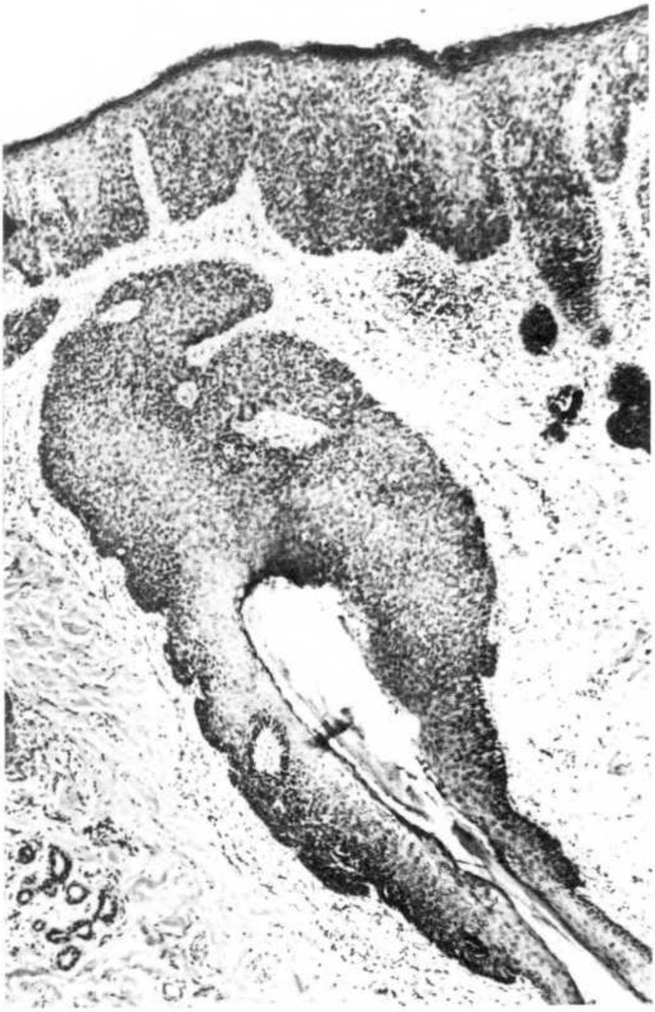

Fig. 2. Intraepithelial neoplasia (VIN III) extends into a hair follicle which lies diagonally across the field. H&E ×75.

Table 2. Characteristics of vulval intraepithelial neoplasia (VIN) in 28 patients with appendicular involvement

Lesion	Number of patients
VIN I	2
VIN II	4
VIN III	18
VIN with single-cell invasion	3
VIN with small carcinoma	1
Total	28

Discussion

In patients with VIN I, II and III with single-cell breaches of the basement membrane and invasive carcinoma extending for ≤3 mm from the basement membrane of the epithelium from which it arises, VIN extends into the skin appendages for ≤4·6 mm from the surface of the epidermis.

Specimens with invasive carcinoma to a depth >3 mm were deliberately omitted as no such lesion would be regarded as suitable for treatment by laser: indeed it is highly probable that

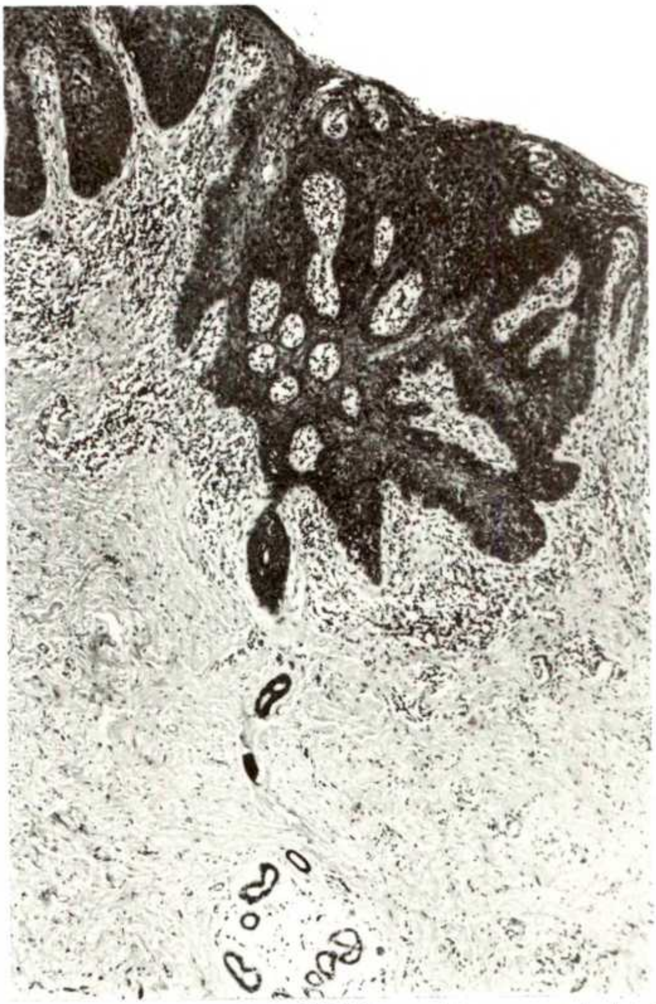

Fig. 3. Intraepithelial neoplasia (VIN III) extends into a sweat gland duct. H&E ×75.

Table 3. Depth of appendicular involvement in vulval intraepithelial neoplasia (VIN)

Lesion	Range in depth of appendicular involvement (mm)
VIN only	0·25–2·5
VIN with single-cell invasion	0·5 –3·0
VIN with small carcinoma	0·75–4·6

even those with invasion limited to 3 mm (stage IA carcinoma) are also unsuitable.

Our experience suggests that eradication of the skin to a depth of 5 mm would therefore eliminate all atypical epithelium in skin appendages but as the appendages themselves may penetrate deeper than this, there remains some doubt as to whether the tissues between 5 and 10 mm should also be destroyed to ensure that no appendages remain. An important practical point which is strongly in favour of the preservation of the deeper portions of the appendages is the improved and more rapid healing which occurs when some of the appendages remain after treatment.

Although VIN extended into the appendages for the greatest distance in those patients with stromal invasion, no matter how slight, this may simply have been a sampling error due to the small number of cases. Nonetheless further examination of this problem, to see whether progression of VIN to invasion is necessarily accompanied by greater involvement of the appendages, is desirable. This study also emphasizes the need for adequate preliminary biopsy of the vulva to ensure that laser therapy is not being inadvertently used for the treatment of early invasive lesions where appendage involvement may be greater than would otherwise have been suspected.

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Management of pseudohypoparathyroidism in pregnancy. Case report

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Case Report

In 1976 a 21-year-old unmarried white nulligravid woman presented to another institution with abdominal pain, constipation, tooth decay and episodes of carpopedal spasm since childhood. She was found to be hypocalcaemic and hypophosphataemic and skeletal X-rays revealed the presence of a cystic lesion in the right ilium. Excision biopsy of this cyst was carried out; macroscopic and microscopic appearances were those of a 'brown' cyst of bone complicating hyperparathyroidism but there were no other radiological signs of this condition. Calcium and vitamin D supplements were prescribed resulting in resolution of her symptoms, but she abandoned this therapy after some months because of nausea.

Symptoms recurred in 1978 and she was admitted to this hospital. It was established that there was no family history of renal or endocrine disease. Examination revealed an intelligent, attractive young woman of normal stature and no physical abnormality other than positive Trousseau's sign. Renal function was normal. Serum calcium was 1·9 mmol/l (normal 2·15–2·65), phosphate 1·6 mmol/l, magnesium 0·88 mmol/l and alkaline phosphatase 75 U/l. Serum albumin was 36 g/l and the parathyroid hormone level (PTH) was 3 m-i.u./ml (normal 0–1·8). CT brain scan demonstrated basal ganglia calcification and skeletal survey was normal but further biochemical assessment revealed urinary calcium excretion of 3·5 mmol/day (normal 2·5–7·5) and phosphate 5·9 mmol/day (normal 11–32). Intravenous infusion of PTH failed to produce the normal phosphaturic response or a rise in urinary cyclic adenosine monophosphate (cAMP) concentrations. Thus a diagnosis of pseudohypoparathyroidism was confirmed.

She again enjoyed a prompt clinical response to re-introduction of calcium and vitamin D supplements with restoration of serum calcium and phosphate concentrations to the normal range.

In 1980 she married and at the time of her first pregnancy in 1981 normal calcium levels (Fig. 1) were maintained with oral calcium 0·5 g/day (calcium Sandoz) and 0·5 μg 1·25 (dihydroxy) cholecalciferol (1·25 HCC as Rocaltrol). Pregnancy was, however, complicated by severe nausea and vomiting. Falling calcium levels necessitated an increase of the vitamin D dose to 1·0 μg daily and calcium to 1·0 g/day to maintain serum calcium at or above 2·10 mmol/l. At 39 weeks gestation a healthy female infant weighing 3·5 kg was born by caesarean section because of cephalopelvic disproportion. The vitamin D dose was reduced to 0·5 μg and serum calcium levels remained at 2·25 mmol/l. The infant had serum calcium levels in the range of 2·30–2·40 mmol/l.

A second pregnancy in 1983–1984 was complicated by more severe nausea and intolerance of both calcium containing foods and calcium supplementation above 0·5 g/day. Vitamin D was administered in the form of 1α-hydroxy cholecalciferol (1αHCC) and dosage increments to 1·5 μg became necessary because of falling calcium values. Total serum calcium fell to 2·00 mmol/l through the third trimester (Fig. 1) while ionized calcium levels varied between 1·0 and 1·1 mmol/l (normal 1·14–1·29). A healthy female infant weighing 2·78 kg was delivered by elective caesarean section at 40 weeks; her calcium values were 2·35 mmol/l on several estimations and she had a normal neonatal course. Maternal hypocalcaemia persisted for several weeks, as illustrated by the two postpartum estimations in Fig. 1, despite treatment with 1αHCC, 1·5 μg/day, and oral calcium, 1·0 g/day.

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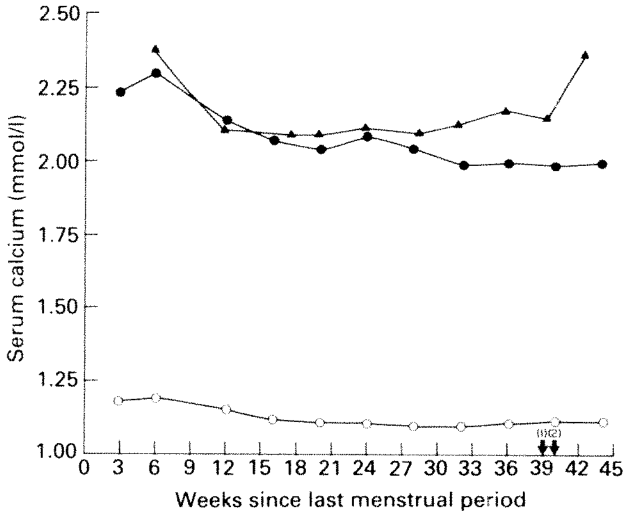

Fig. 1. Total serum calcium values in each pregnancy (▲ pregnancy 1; ● pregnancy 2) and ionized calcium values in the second pregnancy (○). Arrows indicate deliveries.

Discussion

Hypoparathyroidism most often follows thyroid or parathyroid surgery. Much more rarely hypoparathyroidism is due either to primary failure of secretion of PTH (primary hypoparathyroidism) or to failure of target organ responsiveness to PTH (pseudohypoparathyroidism). In this latter case elevated endogenous PTH levels reflect this end-organ resistance (Albright *et al.* 1942). PTH exerts its effect upon target tissues by activating adenylate cyclase and generating cyclic AMP which then serves as the mediator of PTH at the bone and renal targets (Chase *et al.* 1969*a*). In pseudohypoparathyroidism target tissue resistance is confirmed, as in our patient, by failure to elicit a rise in urinary cyclic AMP in response to exogenous PTH (Chase *et al.* 1969*b*).

Although pseudohypoparathyroidism is thought to be of X-linked dominant inheritance a positive family history is frequently lacking. Some affected individuals are of characteristic short stature, have a round face and are mentally retarded but, as our patient shows, this need not be so. Additionally, not all patients exhibit both bone and renal resistance to PTH. Our patient demonstrated complete renal resistance alone; the development of a 'brown' cyst of bone suggests at least partial bone response to high circulating PTH levels.

Parathyroid hormone controls the concentration of calcium and phosphorus in the blood by increasing the rate of calcium absorption from the intestine, increasing the rate of calcium resorption from bone, reducing the rate of calcium excretion in the urine, and increasing the rate of phosphate excretion in the urine. Vitamin D is intricately involved in these actions. Deficiency of PTH or failure of target organ effect results in elevated serum phosphate and reduced serum calcium levels.

Treatment involves administration of calcium and synthetic vitamin D analogues, whilst encouraging a calcium-rich diet with the aim of maintaining normocalcaemia. During pregnancy the goal is to prevent symptoms in the mother while ensuring an adequate calcium supply to the fetus which avidly draws calcium from the maternal circulation via active placental transport (Croley 1973). There is no consensus as to what is the safe lower limit of serum calcium but it is possible, by extrapolation from Pitkin's data on physiological hypocalcaemia in pregnancy (Pitkin 1975), to deduce that a maintenance level of 2·10 mmol/l is desirable. Vitamin D is best given as 1αHCC which by virtue of its short half-life is preferable to the longer acting vitamin D_3 in allowing rapid dose adjustment in the event of hypercalcaemia.

Several reports (Goldberg *et al.* 1976; Glass & Barr 1981) document neonatal hyperparathyroidism and rickets consequent upon prolonged maternal hypocalcaemia. However, over-enthusiastic attempts to achieve normocalcaemia with large doses of vitamin D carry the theoretical risk of fetal supravalvular aortic stenosis due to vitamin D intoxication (Friedman & Roberts 1966); this work was in rabbits while reports of hypoparathyroid women treated with large doses of vitamin D in pregnancy have not indicated any adverse fetal effects (Bolen 1973; O'Leary *et al.* 1966).

Hyperventilation in labour may precipitate tetany because of the alkalosis induced and is to be discouraged. Lactation is not recommended because of the high calcium content of milk and consequent drain on total body calcium stores. Total patient compliance with therapy, regular biochemical monitoring and close liaison between physician, obstetrician and paediatrician are desirable.

The newborn infant may demonstrate hyper-, hypo- or normo-calcaemia and only clinical vigilance combined with laboratory measurement, especially in the first 96 h, will avoid fluctuations. Later in infancy, effort should be directed towards early detection of inheritance of the condition in the hope that early treatment would prevent development of cataracts and mental retardation. Serum calcium estimations at 6-monthly intervals for the first 2 years and at yearly intervals until puberty seem reasonable.

In our patient attempts to maintain desirable calcium levels were thwarted by distressing gastrointestinal intolerance to calcium supplementation exceeding 1 g/day. Despite the low maternal calcium levels during gestation both infants were fortunately normocalcaemic at birth, were normal on physical examination and have thrived subsequently.

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Uterine rupture, placenta percreta and curettage in early pregnancy. Case report

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A 32-year-old housewife had presented in her third pregnancy to another hospital at 7 weeks gestation with a history of vaginal bleeding. Ultrasound showed a bulky uterus with a few disorganized echoes and a missed abortion was diagnosed. Despite uterine curettage, the pregnancy continued with clinical and ultrasound examinations at 25 and 29 weeks being consistent with the stated date of the last menstrual period. She booked into St Mary's Maternity Hospital at 26 weeks gestation.

In the past she had had appendicitis with peritonitis at 18 years of age; the first pregnancy, at the age of 30, ended with a spontaneous abortion at 10 weeks followed by uterine curettage. Her second pregnancy required an elective lower segment caesarean section at 38 weeks for persistent breech presentation with a marginally small pelvis.

From 29 weeks in the third pregnancy she complained of left sided abdominal pain requiring two separate hospital admissions. On each occasion the only abnormal finding was some localized tenderness on the left side of the uterine fundus which settled with simple analgesics within 48 h. There was no evidence of revealed or concealed haemorrhage, nor of preterm labour, nor urinary tract infection. At 31 weeks she was readmitted with a sudden attack of the same left-sided abdominal pain. She was then found to be shocked with acute abdominal symptoms and cardiotocographic evidence of fetal distress. The cervix was closed.

A provisional diagnosis of caesarean scar rupture or possibly concealed placental abruption was made and she had an immediate laparotomy through a Pfannenstiel incision. This revealed a haemoperitoneum of 2·5 litres with an intact lower segment scar. The origin of the bleeding was a rupture 3 × 2 cm in the dome of a localized bulging of the fundus. A severely cyanosed male infant weighing 1·71 kg was extracted through a lower transverse incision. The amniotic fluid was clear and the placenta was firmly adherent to the fundus. A total abdominal hysterectomy with left ovariectomy was performed and 6 units of blood transfused. Postoperative recovery was uneventful and the infant was discharged at 7 weeks, weighing 2·5 kg.

The hysterectomy specimen consisted of a uterus and left ovary. There was a smooth protuberance of the uterine wall 11 cm in diameter which extended from just to the right of the midline of the fundus to the left ovarian ligament (Fig. 1). In the centre was an area of deficient serosa 3 × 2 cm with an associated haematoma. Sectioning the uterus showed the protuberance to correspond to the placental site with the uterine rupture in the centre. The placenta was firmly adherent to the thinned myometrium which gradually thickened from the rupture in a centrifugal manner to reach normal thickness at the margin of the placenta (Fig. 2). No localized

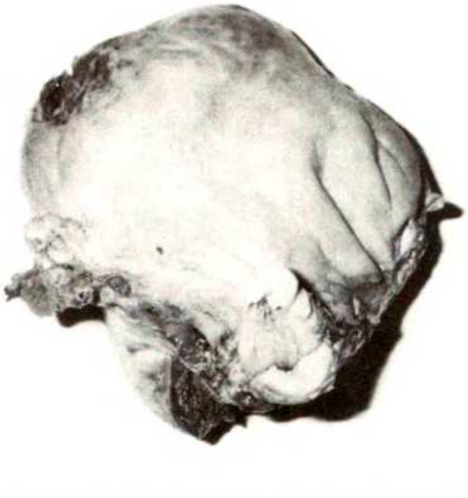

Fig. 1. Posterior aspect of opened uterus showing tumour of fundus and site of rupture.

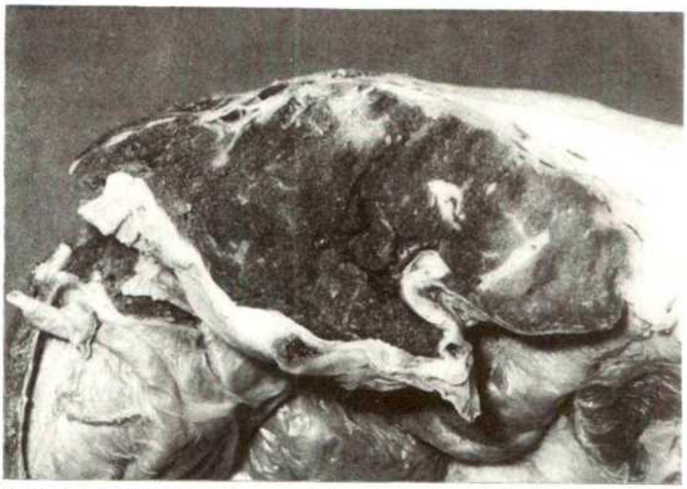

Fig. 2. Gradual thinning of myometrium from edge of chorionic plate (right) to site of rupture (top left). Tissue has been removed at the site of artefactual laceration on the left.

extension of the placental villi into the myometrium was identified. The lower segment incision was 2·5 cm from the placenta and no scar in the region of the section was seen. There appeared to be no congenital structural abnormality of the uterus.

Histology

A section of the curettings obtained from the previous hospital showed decidua alone. Although no placental or myometrial tissue was identified, only part of the tissue was examined histologically. Sections taken from the hysterectomy specimen showed a complete absence of decidua at the placental site, but beneath the peripheral placental membrane occasional remote foci of decidua were identified. Chorionic villi were present at the serosal surface and Nitabuch's layer was interposed between the placental tissue and the myometrium. No trophoblastic hyperplasia and no evidence of scarring from previous myometrial damage was seen.

Discussion

Several of the factors associated with placenta accreta (Fox 1972) were present in this patient. Her age is in the peak incidence group and she was in her third pregnancy. Both previous curettage and caesarean section had been performed. Although the placenta was implanted away from the caesarean scar, this was also seen in six out of 26 patients with placenta accreta who had previously had a caesarean section. No comment, however, was made as to the site of the scar relative to the placenta in the majority of patients in the literature reviewed by Fox (1972). Neither a congenital uterine abnormality nor any difficulty in removing the placenta had been noted at the previous caesarean section. Even though placenta accreta is not uncommonly accompanied by uterine rupture ($\simeq 14\%$), it is an infrequent event compared to other causes of uterine rupture (Schrinsky & Benson 1978).

The presence of placental tissue at the serosal surface and the histological appearances fulfill the criteria for placenta percreta (Meyer 1955). We have been unable to find any report of either curettage during pregnancy being followed by placenta percreta in the same pregnancy or of uterine rupture occurring with a gradual dilatation and thinning of the uterine wall overlying a placenta percreta. This unusual combination of events suggests that the two may be linked. Furthermore, in placenta percreta there are one or more abrupt extensions of chorionic villi infiltrating into the myometrium rather than a gradual loss of myometrium so that villi are situated in the serosa as in this case.

Decidual deficiency is considered to predispose to the development of placenta accreta. Decidua was removed in early pregnancy and was extensively absent at term. The duration of symptoms and presence of an intact placenta below the site of rupture suggest that the process leading to haemorrhage was gradual. Even if the curettage was directly responsible for the initiation of this lesion, the subsequent growth of the placenta and associated uterine changes would probably have masked the original trauma to the decidua and myometrium. Myometrial damage must be an essential antecedent of a lesion of this nature but that is difficult to prove in the later months of pregnancy, in the absence of scar tissue. However, since examination of uteri removed for other reasons, which have undergone caesarean section in the past, often show little evidence of the previous surgery, it is hardly surprising that no scar tissue was found in this case.

A localized protuberance of the uterine wall may also be seen in true sacculation of the uterus. Although usually fundal and containing all or part of the placenta it differs from this case in that it is characterized by an ovoid structure, the wall of which measures 1–2 mm and connects by a small aperture to the pregnant uterine corpus. It may also be complicated by rupture (Rubovits 1951; Fletcher Shaw 1930).

It is difficult to escape the conclusion in our case that the curettage, while not disturbing the pregnancy, damaged decidua and myometrium near to the nidation site to such an extent that the development of the conceptus led to gradual aneurysmal distention of the placental bed, placenta percreta and ultimate rupture. This must be a rare complication of inadvertent curettage performed in early pregnancy.

Acknowledgments

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Abnormal uterine bleeding as a presenting sign of metastatic signet ring cell carcinoma originating in the breast. Case report

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Case report

A 49-year-old married housewife was admitted to the gynaecology service at the Soroka Medical Centre, Beer-Sheva, Israel, in August, 1983 with the complaint of heavy and prolonged menses with cyclic irregularity which had begun 2 years previously. Menarche had occurred at 14 years of age. Menses, until 2 years ago, had been regular with a 28 day cycle and flow lasting 4 days.

In April 1975, she had a right radical mastectomy for invasive carcinoma of the breast. There was no detectable lymph node involvement at the time of surgery. No ancillary radiotherapy or chemotherapy was given.

Physical examination at the time of admission revealed a thin woman with normal vital signs and no evidence of recurrent tumour at the site of the previous mastectomy. The opposite breast and axilla were also free of palpable masses. Pelvic examination revealed an enlarged uterus, the size of an 8 week pregnancy, which was firm anteverted and non-mobile. The pelvic floor had a hard, rigid consistency. The vagina was studded with many small nodules 2–3 mm in diameter. A fractional curettage demonstrated metastatic tumour in the endometrium. The endocervical portion of the specimen was free of tumour. Complete radiological and endoscopic assessment of the entire gastrointestinal tract failed to reveal the presence of any neoplasia. Intravenous pyelography showed right lower ureteric obstruction with right hydroureter and hydronephrosis. The left ureter and kidney were unremarkable. Ultrasound examination of the pelvis revealed a left ovarian cyst about 5 cm in diameter. No metastases could be detected by liver scan. Abdominal and pelvic computerized tomography (CT) scan confirmed the findings obtained from the other examinations. Bone scan showed probable metastatic lesions at D_{12} and in the frontal bone.

At laparotomy the pelvic and abdominal peritoneal and serosal surfaces were studded with innumerable small tumour nodules measuring 2–3 mm in diameter. Survey of the gastrointestinal tract revealed no intrinsic lesions. The lower part of the right ureter was embedded in a tumour mass at the right pelvic floor; the right kidney was markedly enlarged. In view of the extensive metastatic tumour, a conservative approach was adopted and only a left salpingo-oophorectomy was performed. Several omental biopsies were taken.

The patient's immediate postoperative course was uneventful and she was discharged home on the eighth postoperative day. Because of the histopathological findings and the results of the examination for sex steroid receptors, it was decided to treat the patient with the anti-oestrogenic drug tamoxifen, 40 mg/day. Almost 1 year later, she is alive, feeling well, but has a stable metastatic malignant disease.

Pathology

Curettings obtained from the endometrium showed extensive infiltrative permeation of the endometrial stroma by innumerable individual tumour cells, many of which appear in the form of typical signet ring cells (Fig. 1). The histopathology sections of the omentum, left ovary and fallopian tube, showed metastatic signet

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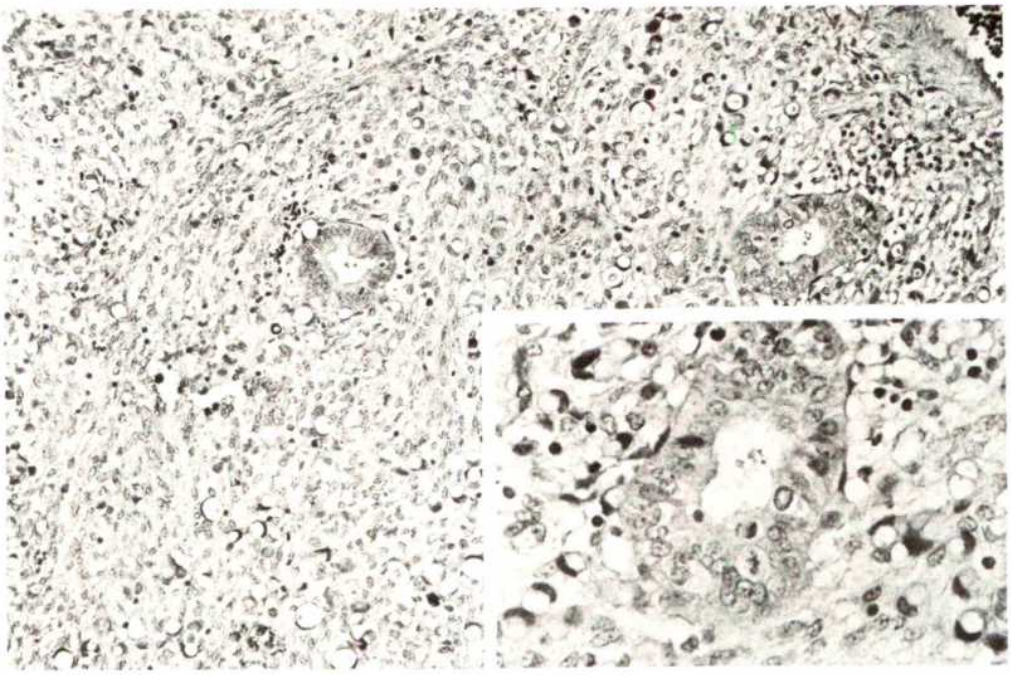

Fig. 1. Tumour metastatic to the endometrium showing extensive stromal permeation by tumour cells of the signet ring cell type (haematoxylin–eosin × 160). Insert: Close-up of endometrium showing stromal invasion by metastatic signet ring cells (haematoxylin–eosin ×400).

ring cell type adenocarcinoma (Fig. 2).

Review of the breast biopsy and mastectomy specimen revealed areas of in-situ and invasive lobular carcinoma with numerous signet ring cells infiltrating the breast stroma (Fig. 3*a* and *b*). Mucicarmine stain for mucin substances was positive in all of the above mentioned specimens.

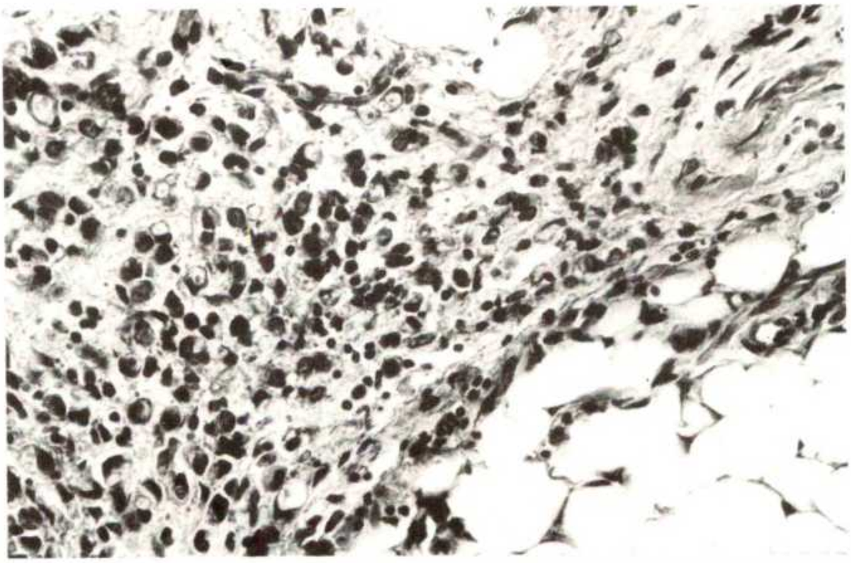

Fig. 2. Metastatic tumour in the omentum showing the same type of neoplastic cell infiltration as seen in the breast. Numerous signet ring cells were identified at this metastatic tumour site (haematoxylin–eosin ×200).

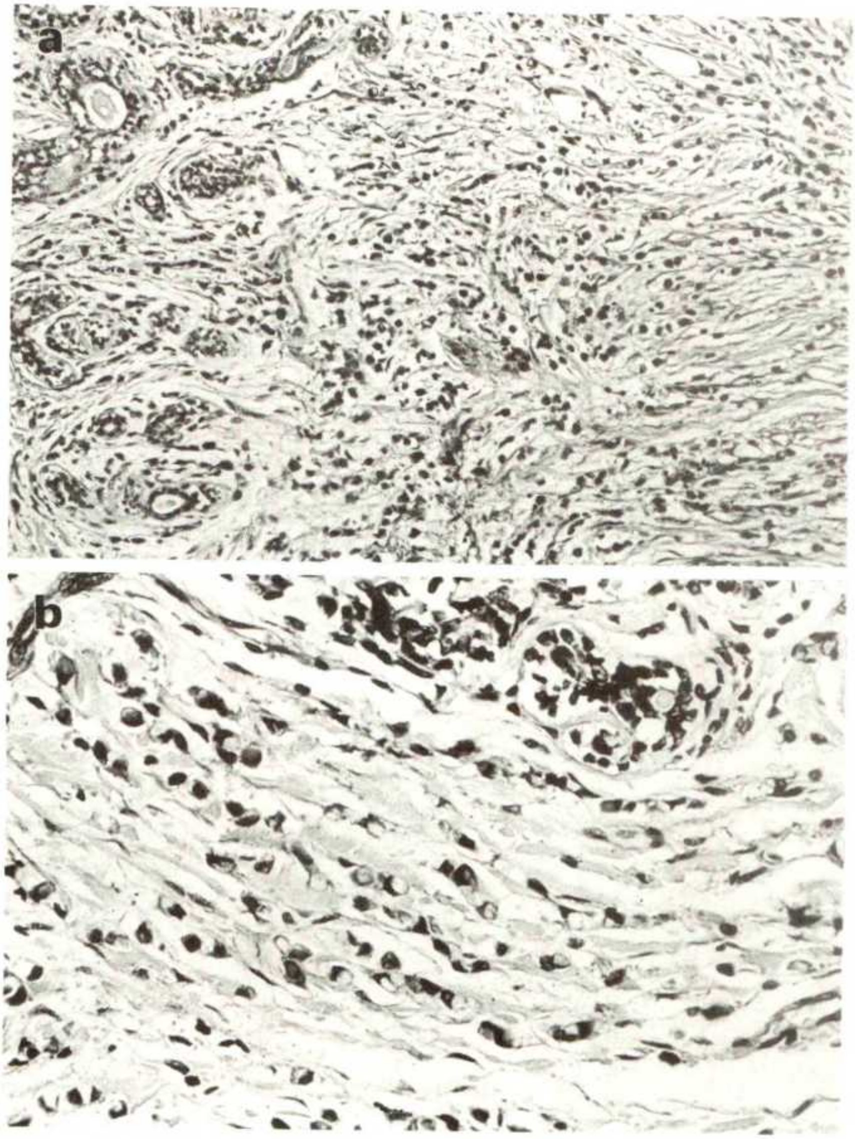

Fig. 3. (*a*) Invasive carcinoma of the breast. Tumour cells infiltrate the breast stroma in an 'Indian file' fashion typical of invasive lobular carcinoma (haematoxylin–eosin ×125). (*b*) Tumour cells of the original breast tumour show a remarkable frequency of signet ring type cells among them (haematoxylin–eosin ×200).

Examination of one of the omental tumour lesions for sex steroid receptors revealed a level of 4·6 fmol/1·0 mg protein and 24 fmol/1·0 mg protein for oestrogen and progesterone receptors respectively (values >3 fmol/1·0 mg protein are considered positive in our laboratory).

Discussion

Metastates to the uterus from extragenital cancers are rare and the first report dealt with a malignant melanoma (Legg 1878). Only a few series of cases have been reported, the largest of which was by Kumar & Hart (1982). Extragenital tumours metastasizing to the uterus appeared in the following order of frequency: breast (42·9%), colon (17·5%), stomach (11·1%), pancreas (11·1%), gallbladder (4·8%), lung (4·8%), melanoma of skin (3·2%), urinary bladder (3·2%) and thyroid (1·6%) (Kumar & Hart 1982). The above distribution may merely reflect the prevalence of the various extragenital malignant tumours in women (Post *et al.* 1966). When the anatomical distribution of metastases within the uterine corpus, in hysterectomy and autopsy cases, was examined it was found that the myometrium only was involved in 63·5%, the myometrium and endometrium in 37·7% and the endometrium only in 3·8% (Kumar & Hart 1982). Uterine leiomyomas may also be the site of metastasis (Weingold & Boltuch 1961; Banooni *et al.* 1971; Kumar & Hart 1982). It has been emphasized that metastasis to the uterus from extragenital tumour sources is but a local manifestation of more widespread dissemination. Stemmerman (1961) suggested that uterine metastases are most often caused by secondary local lymphatic spread from earlier appearing ovarian metastases. Spread is probably haematogenous when the ovaries are not affected.

Abnormal uterine bleeding is often the first sign of metastatic disease following surgery for primary extragenital tumours (Stemmerman 1961; Klaer & Holm-Jensen 1972; Pradhan & Jussawalla 1979). The time interval between the diagnosis of the primary cancer and the appearance of abnormal uterine bleeding may be up to 8 years (Casey & Shapiro 1974; Jaffrey *et al.* 1976; Takeda *et al.* 1978). Rarely is the primary extragenital cancer discovered after the appearance of uterine metastases (Kumar & Hart 1982). In addition to the more common aetiologies for abnormal uterine bleeding, the gynaecologist must always consider the possibility of metastatic tumour. This is true especially in the case of a women with a history of malignant disease.

The majority of metastatic signet ring cell carcinomas originate from the gastrointestinal tract, usually the stomach (Leiberman *et al.* 1975). Complete assessment of our patient's gastrointestinal tract failed to disclose any primary gastrointestinal tumour. In view of the histopathological finding upon review of the breast biopsy and mastectomy specimen and in view of the positive values for oestrogen and progesterone receptors, it is our opinion that this patient's metastatic uterine tumour originated in her breast cancer. Of particular interest is the unusual histopathological nature of the primary breast tumour—signet ring cell carcinoma—and the protracted time interval of 8 years between her initial breast surgery and the appearance of uterine metastases.

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Phaeochromocytoma of the broad ligament. Case report

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Case report

A 51-year-old woman was found to have a right adnexal mass during vaginal examination prior to a routine cervical smear. She had had four normal deliveries and had a normal menstrual cycle. Her medical and family histories were unremarkable.

Physical examination showed no other abnormality and her blood pressure was 150/90 mmHg. At laparotomy, her uterus was slightly enlarged but regular and mobile. Both ovaries and tubes were normal. A discrete, mobile, spherical mass was present within the layers of the right broad ligament, between the meso-ovarium and the round ligament. No other abnormality was detected in the pelvis or retroperitoneum and no lesions were identified in the suprarenal or para-aortic areas. Because of the close relation between the mass and the uterine appendage, the latter was removed together with the mass, which appeared benign and was sent for frozen section. Postoperatively the patient made an uneventful recovery. Following the histological diagnosis of phaeo-

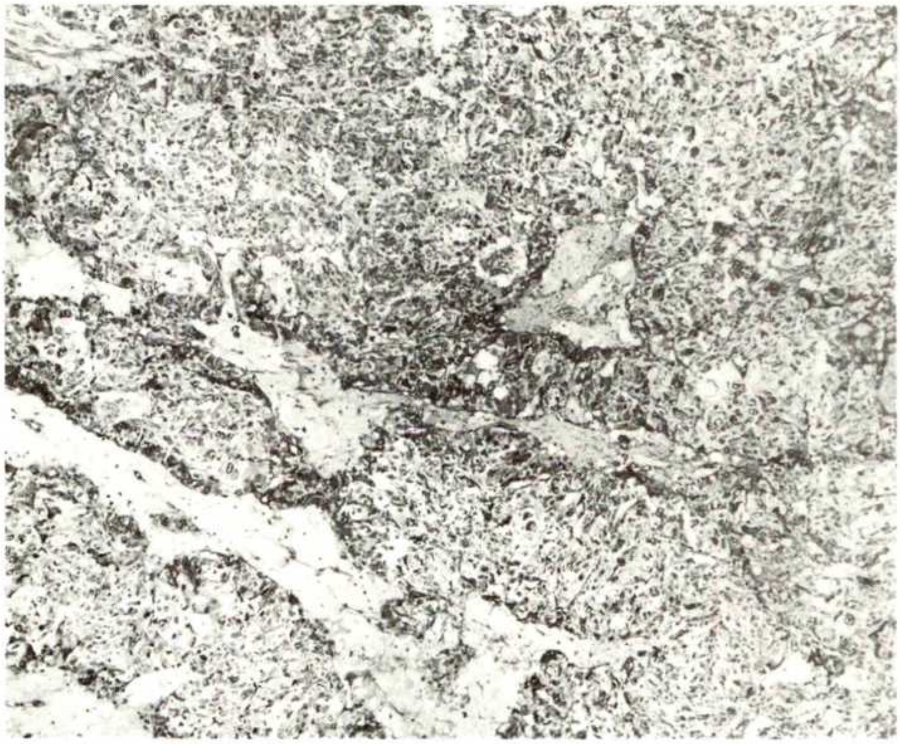

Fig. 1. Section of the tumour showing tumour cells arranged in nests, punctured by thin walled sinusoids. Haematoxylin and Eosin ×57.

chromocytoma the patient had, on three occasions, a 24-h urine specimen investigated for vanillyl mandelic acid, noradrenaline and dopamine levels. The results were within normal limits. She was well when seen 6 months after the operation. There had been no change in the patient's blood pressure after removal of the tumour.

Pathological findings

The surgical specimen was sent unfixed and consisted of a firm red nodule 5·0 × 4·5 × 3·0 cm with a central cyst 2·0 cm in diameter. The diagnosis of phaeochromocytoma was suspected on frozen section and when a piece of the tumour was put in chromium salt solution the tumour became brown-black, indicating a positive chromaffin reaction. The rest of the tissue was fixed in 10% buffered formalin.

Light microscopy. Sections from the chromate-fixed tissue showed a strongly positive chromaffin reaction. The haematoxylin–eosin stained sections showed the typical appearance of a phaeochromocytoma. The tumour was composed of large cells which possessed a faintly granular cytoplasm and were arranged in solid masses; the stroma was scanty and vascular (Fig. 1). Reticulin stain confirmed the alveolar pattern of cell nests. Sections stained by the Grimelius silver method showed a positive argyrophil reaction.

Electron microscopy. A portion of formalin-fixed tissue was diced into 1-mm cubes, post-fixed in osmium tetroxide, dehydrated and embedded in epon. Thin sections (1 μm) were cut and stained with toluidine blue and examined by light microscopy. Ultrathin sections were examined in an AE1 corinth 500 electron microscope. The neoplastic cells contained numerous dense core vesicles, typical of phaeochromocytoma (Fig. 2).

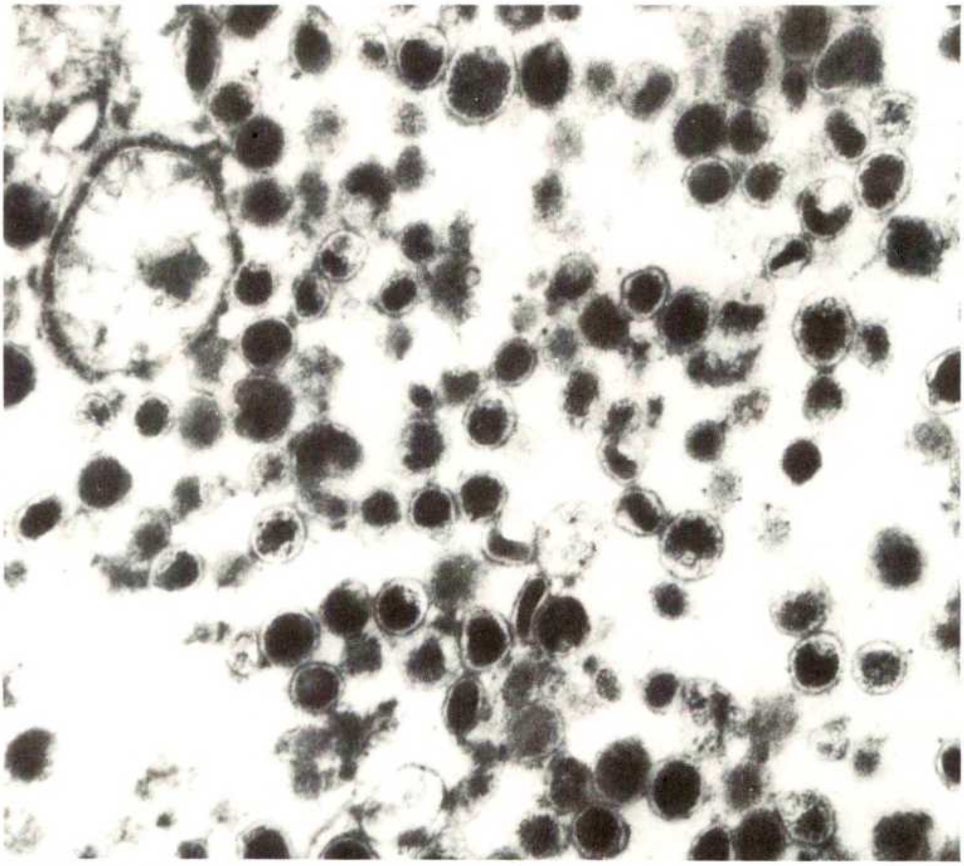

Fig. 2. Electron micrograph of the tumour showing dense core granules ×40 000.

Discussion

Approximately one-sixth of phaeochromocytomas are extra-adrenal and these affect the organ of Zuckerkandl, bladder, para-aortic region, chest, neck and bladder (Melicow 1977). Occasionally these tumours have been reported in the ovary (Fawcett and Kimbell 1971), vagina (Plate 1955), pericardium (Saad *et al.* 1983) and kidney (Rothwell *et al.* 1983). To our knowledge only one case has been reported in the broad ligament (Aron *et al.* 1980). This patient had a typical history of intermittent hypertension with raised catecholamine levels and the diagnosis of phaeochromocytoma was made preoperatively.

These extra-adrenal abdominal phaeochromocytomas develop from extramedullary chromaffin tissue. This is found in association with the sympathetic chain around the aorta and its branches and it is presumably from such tissue in the broad ligament that the present lesion arose.

In a previous study (Melicow 1977) 17 out of 100 patients with phaeochromocytoma had a clinically 'silent' tumour. Those in whom the diagnosis was missed and who had exploratory surgery often died because of the sudden release of large amounts of catecholamines producing hypertension and leading to acute heart failure or intracerebral haemorrhage.

In our patient the tumour was clinically silent and no pre-operative diagnosis was made. Exploration of the tumour could have resulted in serious complications, had it been functioning.

Primary paraovarian tumours are uncommon and are usually leiomyomas or rarely epithelial tumours or sarcomata (Talerman 1982). We believe phaechromocytoma, although rare, should be clinically considered in the differential diagnosis of a paraovarian mass to enable a correct pre-operative diagnosis to be made wherever possible.

Acknowledgments

Our thanks to Professor Donald Heath, University of Liverpool, Department of Pathology for the Electron microscope facilities and photomicrographs and Miss Angela Taylor and Miss Janet Simpson for typing the manuscript.

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CORRESPONDENCE

Thromboxane A_2 and prostacyclin levels in molar pregnancy

Dear Sir,

Roy *et al.* [*Br J Obstet Gynaecol* (1984) **91,** 908–912] recently reported an interesting study on prostacyclin (PGI_2) in molar pregnancy showing that molar intravesicular fluid had very high levels of 6-keto-$PGF_{1\alpha}$, a major PGI_2 metabolite. They reported no corresponding increase in maternal plasma 6-keto-$PGF_{1\alpha}$. Since they did not determine normal maternal plasma PGI_2 metabolite levels with their assay, this claim is hard to substantiate, as the variation between different radioimmunoassays (RIA) for PGI_2 metabolites is enormous. RIA is of great value in studying comparative values of PGI_2 metabolites using the same assay, but cannot give absolute values and therefore comparisons between groups studied by different RIA methods, as Roy *et al.* (1984) have done for their normal maternal plasma control range, is not possible. They also report that a series of normal amniotic fluids had a mean PGI_2 metabolite level of 34 (SD 17) pg/ml, suggesting that PGI_2 is normally present in amniotic fluid in the second trimester. We have measured PGI_2 metabolites in amniotic fluid and maternal plasma in 27 pregnancies between 18 and 22 weeks gestation. All patients were undergoing amniocentesis for genetic analysis or investigations for a possible neural-tube defect. We used a RIA previously described (Belch *et al.* 1983; Greer *et al.* 1985) with a lower limit of sensitivity of 5 pg/ml, inter- and intra-assay variations were both less than 10% and recovery of added 6-keto-$PGF_{1\alpha}$ was 95 (SD 9)%.

Of the 27 pregnancies 26 were normal and in one the fetus had a myelomeningoccele. In all the normal patients amniotic fluid PGI_2 metabolities were undetectable whereas the normal maternal plasma level was 15·8 (SEM 0·7) pg/ml, this compares with our previously reported mean level of 15·5 (SEM 1·05) pg/ml for normal second trimester pregnancy (Greer *et al.* 1985). In the one abnormal pregnancy, however, amniotic fluid PGI_2 metabolites were 62 pg/ml and the maternal plasma level was 170 pg/ml, the highest we have ever recorded in pregnancy. The reason for the high level is unclear but may be related to exposure of damaged highly vascular, neural tissue to amniotic fluid, and to placental transfer of the PGI_2 metabolites. While further studies on pregnancies complicated by neural-tube defects are required to substantiate this finding, it raises the possibility that high PGI_2 metabolite levels may be a marker for such defects. In addition it suggests that PGI_2 metabolites can cross into maternal plasma. We would therefore urge Roy *et al.* (1984) to determine their own normal control range, as they may find that maternal plasma PGI_2 metabolites are high in molar pregnancy.

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BOOK REVIEWS

LHRH and Its Analogs: Contraceptive and Therapeutic Application edited by B. H. Vickery, J. J. Nestor Jr & E. S. E. Hafez. MTP Press Limited, Lancaster, 1984, 470 pages with figures and tables. £45.00

It is now over a decade since LHRH and its analogues has been available for investigation and use. During this time there has been an explosion of chemical, physiological and pharmacological data on this hypothalamic peptide, and some 1500 agonist and antagonist analogues of LHRH have been synthesized to overcome the problems of the uses of native LHRH—that is its very short half-life. In the past decade the research on LHRH and its analogues has been particularly impressive as it presents a very successful chemical and pharmacological research story. Chemical studies have resulted in LHRH analogues which are highly potent and long-lived with receptor affinities greater than that of LHRH. Pharmacological investigations have covered an impressive list of clinical applications, many of which are currently being tested on patients—of relevance to gynaecologists are the implication of native LHRH for induction of ovulation, the use of analogues to suppress pituitary ovarian function to treat endometriosis, precocious puberty, polycystic ovary syndrome, menorrhagia and uterine fibroids, as well as the fascinating potential for utilizing these analogues to treat prostatic carcinoma in the male and breast carcinoma in the premenopausal female. The book reports a symposium held in October 1982 at which many of the now renowned figures involved in research on LHRH presented data. The various sections include ones related to the chemistry and basic reproductive properties of LHRH and its analogues, the reproductive physiology and pharmacology of the agents in laboratory animals, and extra hypophysial parameters of the releasing hormone. The book goes on then to review the use of the releasing hormones analogues as contraceptive agents in the female and male and an extensive review of the human applications of these agents. The book is certainly the most up-to-date tome on this agent, contains a well balanced review of the topic and a veritable list of pertinent references. It would therefore be of interest to anyone concerned in the use of these agents in a research or clinical manner, but perhaps containing too much research data for individuals not wishing to read as deeply around the topic, e.g. those working for the Membership.

R. W. Shaw

Pregnancy, Diabetes and Birth. A Management Guide Dorothy Reycroft & Hollingsworth. Williams & Wilkins, London, 1984, 166 pages illustrated, £32.00

I approached this guide to the management of the pregnant diabetic with good will. It is concise, freely illustrated, the product of a single author rather than a committee, and comes from a department where diet is considered an important part of treatment The references are well selected, up to date, and pay respect to European research. The single best feature is a composite colour photograph of the somatotypes associated with carbohydrate intolerance in pregnancy. I assume the book is intended as a practical guide for non-specialist units where diabetes complicating pregnancy is an occasional problem. As such it does not cross the Atlantic very well. It is annoying and potentially confusing to have to convert blood glucose levels from mg/dl to mmol/l. 'Regular insulin' means soluble insulin, but what are 'Glucola' and 'graham crackers'? There are five pages of photographs of insulin pumps. More photographs are wasted on the technique of blood glucose stick testing and the meters available in the USA. In chapter 2 the author's studies of 'meal tolerance testing' in non-diabetics show improved glucose homeostasis in the third trimester versus the second. This observation appears incompatible with the metabolic changes of 'normal pregnancy' described in chapter 4, but evokes no comment. On details of management there will always be disagreements, but few British units would consider the screening for gestational diabetes recommended here to be justified. In the chapter on timing of delivery it is confusing to find the evidence that biophysical tests often result in false-negatives carefully reviewed, followed by a recommendation that these tests should nevertheless be used. An interesting book and there is certainly a need for a practical guide of this type—but I could not wholeheartedly recommend this one.

Robert Fraser

Advances in Paediatrics Vol. 30 edited by L. A. Barness. Year Book medical Publishers Inc., Chicago, 1984, 712 pages with figures and tables, £52.50

Yearly publications can either aim to cover recent advances across a subject as a whole, as with the 'Annual Review' series, or they can be a repository for timely review articles of excellence. *Advances in Paediatrics* to my mind often falls uncomfortably between these two alternatives, and volume 30 illustrates the problem. There are 18 chapters which cover a wide range from the place of pulmonary artery catheterization in paediatric intensive care, via bone marrow transplantation, to the sudden infant death syndrome. Some chapters are excellent, notably one on the physically handicapped child, which is both helpful and moving, and which would be worth reading by anyone who has to do with a family in which there is a handicapped child. At the other extreme is a jargon-ridden chapter on advances in paediatric pharmacology and toxicology, demonstrating a number of contradictions and unreferenced assertions. There are 10 chapters that might be of interest to the obstetrician, including an extensive but rather weak review of nutritional physiology in pregnancy, a good overview of the sudden infant death syndrome, and several chapters of relevance to neonatal health and disease. A 10/18 overlap with paediatrics surely reflects the convergent course of the two historically separate clinical subjects.

R. D. H. Boyd

Prostaglandins and Fertility Regulation. Advances in Reproductive Health Care edited by M. Toppozada, M. Bygdeman & E. S. E. Hafez. MTP Press, Lancaster, 1984, 157 pages with figures and tables, £45.00

This volume is one of a series entitled 'Advances in Health Care' edited by E S. E. Hafez. It first examines the biochemical and pharmacological knowledge of prostaglandins on the uterus, cervix and ovary and second describes the clinical application of prostaglandins and their analogues for early abortion, cervical priming prior to evacuation and for mid-trimester abortion. The contributors who are from Europe and the USA are all well known for their work in this field. The chapters are comprehensive and succinct with good bibliographies. The book is to specialized to be of general interest to obstetricians and gynaecologists. However, it forms a useful collection of up-to-date information for the reproductive scientist or clinician with a special interest in prostaglandins and their role in the reproductive processes. At £45 it seems considerably overpriced.

M. G. Elder

Practical Colposcopy Second Edition by Rene Cartier. Laboratorie Cartier, Paris, 1984, 310 pages with figures and tables, no price given.

There can be very few books that are classed as classic in that they make a significant contribution to the subject that they cover. This text is a classic because any colposcopist practising his art must at sometime read it and should be conversant with many of its contents. Indeed Professor Wilbanks in the foreword to the second edition comments on the art of colposcopy as presented by Rene Cartier, 'a true artist of correlative colposcopy, cytology and histopathology'. Professor Cartier's first edition published nearly 8 years ago had become the standard work for all colposcopists. The photographs are certainly the most beautiful that have ever been produced on the cervix and to these are linked the most elegant coloured diagrams. The histology and cytology is also elegantly displayed and all in all it makes for a most classical and beautiful text. There are various methods and techniques within the book that will be foreign to many readers. Professor Cartier's insistence on the diathermy loop biopsy system, is unique but certainly the resulting specimens are precise and easy to interpret. Even if one does not agree with all his concepts of the practise of colposcopy, the mere fact that he is able to document them allows the reader the opportunity to form his own opinions. No matter how experienced the colposcopist, the book holds many delights for him. Although colposcopy is a practical diagnostic technique it is a method that should be known in its theoretical aspects by all gynaecologists. If it were possible this atlas would be made compulsory reading for all of us who take a cervical smear from the cervix be they, paramedical staff, nurses, midwives, or doctors. It is a book that can be recommended. It is indeed a classic.

A. Singer

Prenatal Diagnosis Proceedings of the Eleventh Study Group of the Royal College of Obstetricians and Gynaecologists, September 1983, edited by C. H. Rodeck & K. H. Nicolaides, published jointly by the Royal College of Obstetricians and Gynaecologists and John Wiley and Sons, Chichester, 1984, 298 pages with figures and tables, £16.50 plus postage (£7.50 plus postage to Fellows and Members of the RCOG)

Counselling about congenital malformations no longer is restricted to the possibilities of occurrence or recurrence of an abnormality. In many cases it can now include discussion about diagnosis of the problem sufficiently early in pregnancy to allow consideration of termination. Such prenatal diagnosis became effective and accurate with the advent of ultrasound; increasingly so as its technology improves. Informative grey-scale pictures are diagnostic in many cases, in others they increase the safety of amniocentesis or chorionic villus sampling. The range of conditions which can be diagnosed from tissue obtained by these techniques is widening rapidly with increasingly sophisticated methods of analysis. Treatment *in utero* also has become a clinical reality, although which fetuses will benefit from it has yet to be decided. The diagnosis of chromosome abnormalities has been commonplace for some time but uncertainties in the diagnosis of spina bifida, congential heart disease and other structual abnormalities have been reduced in the last decade. Some inherited metabolic diseases and other problems can also be diagnosed antenatally so that now a couple (at risk or not) start a pregnancy confident that congenital anomalies can be diagnosed in time for the pregnancy to be terminated if they wish. This confidence is not always justified because many conditions still cannot be diagnosed and no system of screening is perfect in its organization. Nonetheless, clinical science is moving toward the reality of public expectation. The birth of many severely abnormal babies will be prevented by the use of the technology now available, but these are likely to be replaced by apparently healthy carriers of abnormal genes who will increase the pool of genetic abnormality in the population. This problem is touched on by a discussion of the social consequences of screening for thalassaemia in *Prenatal Diagnosis,* and will become an increasingly important problem for any population practising early pregnancy diagnosis. This book is the record of a meeting of experts convened by the RCOG. Both formal papers and discussion are included: the former are informative and the latter illuminates them helpfully for both the cognoscenti and the general reader. An overview of prenatal diagnosis starts the reader on his way which finishes with a chapter on its social implications. Between these there is a description of the techniques currently used, and a primer on DNA analysis and its application in this field. The structural and functional abnormalities which can be diagnosed are reviewed: detection of haemoglobinopathies, of some inherited metabolic diseases, of haemophilia and of neural-tube defects are now commonplace, but informed parents may seek advice about muscular dystrophy, cystic fibrosis, or fetal immune problems: all are here. Risk populations and their recognition are described. Counselling of those who have already had an abnormal child requires accurate post-mortem diagnosis; the techniques for this are reviewed in detail. The outlook for future developments in prenatal diagnosis and fetal treatment are discussed. This book will not tell you how to get a ticket for a gene library or what song ultrasound sings to the fetus, but is is an excellent introduction to the current possibilities and problems of prenatal diagnosis. Many will probably read most of it, but it also will be kept for reference and may be consulted for years after its publication.

I. R. McFadyen

Perinatal Mortality Survey. Scotland 1977–1981 Edited by G. M. McIlwaine, F. Dunn, R. C. L. Howat, M. Smalls, M. M. Wyllie & M. C. MacNaughton. Available from: University of Glasgow Social Paediatric and Obstetric Research Unit, 64 Oakfield Ave, Glasgow G12 8LS, £3.00

The Scottish Perinatal Mortality Survey started in 1977 as a research project. Since then it has continued to develop and change until it now forms part of Scotland's routine data collection system. As its title suggests this volume summarizes and discusses the data collected about perinatal deaths during the years 1977 and 1979–1981 It is noteworthy that unlike in Northern Ireland the authors did not find much sign of any under-registration of perinatal deaths. Having presented their extensive and interesting data about stillbirths and early neonatal deaths, the authors go on to make the case for a wider measure of reproductive loss which would cover both spontaneous and therapeutic abortions from 20–27 weeks of pregnancy as well as birth related deaths in the post perinatal period.

Alison Macfarlane

Books received some of which may be reviewed at a later date

Atlas of Endometrial Histopathology by Gisela Dallenbach-Hellweg & Hemming Poulsen Munksgaard, Copenhagen, 1985, 229 pages fully illustrated, DKr 470.00

The Year Book of Obstetrics and Gynecology 1984 edited by Roy M. Pitkin & Frank J. Zlatnik. Year Book Medical Publishers Inc, Chicago, 1984, 476 pages with figures and tables, £41 50

Infertility (Patient Handbook 22) by Gabor Kovacs & Carl Wood. Churchill Livingstone, Edinburgh, 1985, 68 pages illustrated, £1.80

Manual of Obstetric Anesthesia edited by Gerard W. Ostheimer. Churchill Livingstone, Edinburgh 1984, 424 pages with figures and tables, £26.00

Scientific Basis of Obstetrics and Gynaecology Third edition edited by R. R. Macdonald Churchill Livingstone, Edinburgh, 1985, 520 pages with figures and tables, £35 00

Handbook of Endemic Treponematoses: Yaws, Endemic Syphilis and Pinta edited by P. L. Perine, D R Hopkins, R K. St John, P. L. A. Niemel, G. Causse & G M. Antal. World Health Organization, Geneva, 1984, 59 pages and 68 colour plates, SwFr 20 (Arabic, French and Spanish editions in preparation)

The Critically Ill Obstetric Patient edited by R. W. M. Baldwin & Gillian C. Hanson Farrand Press, London, 1985, 570 pages with figures and tables, £38.30, US$65 00

Special Topics in Endocrinology and Metabolism Vol 6 edited by Margo P. Cohen & Piero P. Foa. Alan R. Liss Inc, New York, 1984, 264 pages with figures and tables, £44.00

Atlas of Obstetric, Gynecologic and Perinatal Ultrasonography edited by Kenneth J. W. Taylor. Churchill Livingstone, Edinburgh, 1985, 433 pages with illustrated plates, £50 00

Drugs and Pregnancy Maternal Drug Handling—Fetal Drug Exposure edited by B. Krauer, F. Krauer, F. E. Hytten & E. del Pozo. Academic Press, London, 1984, 281 pages with figures and tables, £17.00, US$22.00

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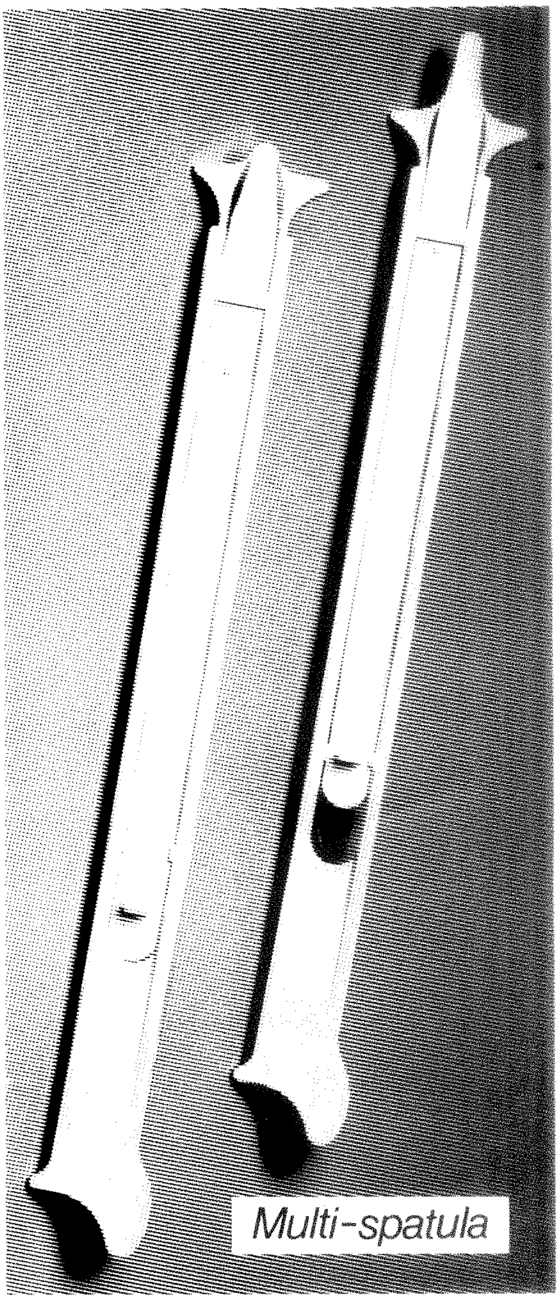

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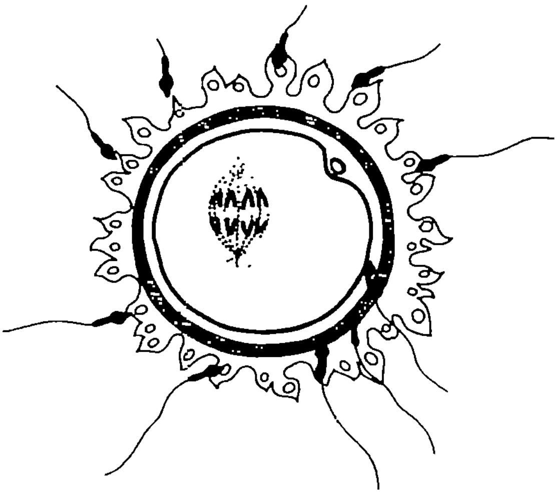

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Manuscripts should contain a statement that the work was approved by the ethics committee of the institution in which it was done and that subjects gave informed consent to the work. The editors reserve the right to reject papers if they consider the ethical justification to be questionable.

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Hytten, F E. & Leitch, I (1971) *The Physiology of Human Pregnancy* 2nd edn, Blackwell Scientific Publications, Oxford, p 26.

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